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The development of novel gold-catalysed indole cascade reactions

Heffernan, Stephen

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The Development of Novel Gold-Catalysed Indole Cascade Reactions

Stephen John Heffernan

A thesis submitted for the degree of Doctor of Philosophy

University of Bath

Department Of Chemistry

May 2012

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“So it goes.” – Kurt Vonnegut

Acknowledgements

After many a crisis of faith, and three and a half years of my life, I am extremely happy to be in this position. And without the help of the people mentioned hereafter I don't think I would have made it this far.

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Cheers!

Abstract

Divided into three distinct research areas, this thesis investigates the synthetic utility of enynones and ynamides towards the formation of biologically relevant structures.

The first volume of work (Chapter 2) describes the gold-catalysed double alkylation of indole by enynones. The [6,5,7]-tricycles formed in this reaction are generally provided in excellent yield with complete regioselectivity. Optimisation of the procedure, a thorough substrate investigation, and mechanistic insights are discussed within.

The gold-catalysed rearrangement of ynamido esters is described in Chapter 3. Following 1,3-acyl transfer, nucleophilic addition of indole to the intermediate allenamide provides a novel enamide scaffold. The substrate scope has been assessed, with high yields provided for most examples.

The final chapter concerns the Ireland-Claisen rearrangement of ynamido esters, with post-rearrangement decarboxylation furnishing aminodienes. Following a substantial optimisation study, a range of ynamido esters were screened, providing a range of functionalised aminodienes in good yield with varying *Z:E* selectivity.

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Abbreviations

Ac	acetyl
app.	apparent
aq	aqueous
Boc	<i>tert</i> -butyloxycarbonyl
Bn	benzyl
br	broad
BSA	<i>N,O</i> -Bistrimethylsilyl Acetamide
<i>n</i> -Bu	<i>n</i> -butyl
<i>t</i> -Bu	<i>tert</i> -butyl
Bz	benzoyl
cod	Cyclooctadiene
d	doublet
DBA	dibenzylideneacetone
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	dichloroethane
DCM	dichloromethane
DMAP	4-dimethylaminopyridine
DMSO	dimethyl sulfoxide
DMF	dimethylformamide
DNsOH	2,4-dinitrobenzenesulfonic acid
dppf	1,1'-bis(diphenylphosphino)ferrocene
dppp	1,3-bis(diphenylphosphino)propane
dr	diastereomeric ratio
DVK	divinyl ketone
EDCi	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
Ee	enantiomeric excess
Et	ethyl
equiv.	equivalents
ESI-MS	electrospray ionisation mass spectrometry
g	gram
h	hour(s)
HOMO	highest occupied molecular orbital

Hz	hertz
HFIP	hexafluoroisopropanol
IMes	1,3-bis-(2,4,6-trimethylphenyl)imidazol-2-ylidene
IPr	1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene
LDA	lithium diisopropylamide
LiHMDS	lithium hexamethyldisilazide
LUMO	lowest unoccupied molecular orbital
m	multiplet
<i>m</i> -	<i>meta</i>
Me	methyl
mg	milligram
μL	microliter
μW	microwave
mL	millilitre
MHz	megahertz
NaHMDS	sodium hexamethyldisilazide
NBS	<i>N</i> -bromosuccinimide
NMR	nuclear magnetic resonance
<i>o</i> -	<i>ortho</i>
<i>p</i> -	<i>para</i>
Ph	phenyl
Phth	phthaloyl
PPA	polyphosphoric acid
<i>i</i> -Pr	<i>iso</i> -propyl
<i>n</i> -Pr	propyl
PVC	polyvinyl chloride
q	quartet
rt	room temperature
s	singlet
t	triplet
Tf	triflate
THF	tetrahydrofuran
TBDPS	<i>tert</i> -butyldiphenylsilyl
TBS	<i>tert</i> -butyldimethylsilyl

TMS	trimethylsilyl
TBAI	tetra- <i>n</i> -butylammonium iodide
TLC	thin layer chromatography
TBAF	tetra- <i>n</i> -butylammonium fluoroide
Ts	tosyl
Z	atomic nuclear charge

1. INTRODUCTION

1.1 Gold

Gold metal has been utilised for many purposes; the most common of which focus on its physical attributes. Elemental gold is a dense, soft and ductile metal with a bright yellow colour, and as such is traditionally considered to be attractive, being made into ornate decorations and jewellery.¹ Gold is also used extensively within the electronics industry due to its electrical conductivity, ductility and also its high resistance towards corrosion and tarnishing.² Historically, gold was also used as part of the monetary system due to its desirability.^{3,4} Although the physical uses and attributes of gold have been well investigated, it was generally perceived to be catalytically inactive, possibly due to the inherent stability of elemental gold, which can exist in its elemental form in nature.

1.2 Transition metal catalysed transformations and gold

The use of transition metals in chemistry has been able to effect many synthetic transformations that would have been otherwise impossible employing traditional organic methods.⁵ The chemistry of the majority of the transition metal complexes is generally well understood and has been well utilised in a variety of transformations including hydrogenations, cross-coupling and metathesis reactions.

There were a number of scattered reports of the catalytic use of gold however they were generally inferior when compared with the use of alternative transition metal catalysts.⁶ However, two observations noted in the 1980s would alter the assumption that gold was catalytically inactive: the low temperature oxidation of carbon monoxide using supported gold catalysts⁷ and the hydrochlorination of ethyne by gold(III) chloride.⁸

1.3 First uses of gold

1.3.1 Low temperature oxidation of carbon monoxide

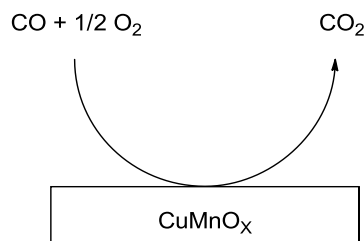


Figure 1 – Traditional oxidation of carbon monoxide with Hopcalite catalysts

The oxidation of carbon monoxide to carbon dioxide is an important industrial process, required during the combustion or partial oxidation of hydrocarbons. Previously, Hopcalite catalysts (mixed oxides of manganese and copper) were used to effect the oxidation of carbon monoxide, however they suffer from poor activity at room temperature, as well as being moisture sensitive.⁹ Alternative transition metals/transition metal catalysts can also be used for this oxidation, but all suffer from either; poor activity at ambient temperatures¹⁰, loss of activity over time¹¹ or restricted applications.¹² Gold composite catalysts prepared by Haruta and Yamada, from the co-precipitation from an aqueous solution of chloroauric acid and the nitrate of various transition metals, were shown to have both significant activity, even at $-70\text{ }^{\circ}\text{C}$, and considerable stability compared to previously used catalysts.^{7, 13} The most active catalyst system, 5 atom% Au/ $\alpha\text{-Fe}_2\text{O}_3$, remained active for seven days after initial usage, compared to just 20 minutes for the most active Hopcalite catalyst.⁷

1.3.2 Vinyl chloride synthesis

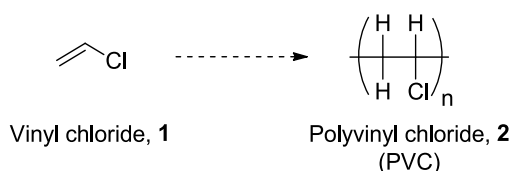


Figure 2 – Structure of vinyl chloride 1 and PVC 2

Vinyl chloride **1** is the monomer required for the formation of polyvinyl chloride **2** (PVC), which was the 4th most produced plastic in 2010.¹⁴ Therefore the efficient formation of vinyl chloride is an important industrial process and was historically carried out by the hydrochlorination of acetylene utilising mercuric chloride supported on carbon as the catalyst.¹⁵ This catalyst becomes inactive over time due to the sublimation of the active component, therefore an alternative catalyst was required.¹⁶

A range of metal chloride catalysts were supported on carbon and gave a range of activities for the hydrochlorination reaction.^{17, 18} Mechanistic insights into the reaction indicated that the rate-determining step involves the addition of HCl to the metal acetylene complex and it can therefore be assumed that the stability of the metal acetylene complex will greatly affect the catalytic activity of each metal chloride.¹⁹

Attempts to correlate the relative catalytic activities of each complex, with a number of molecular parameters were undertaken to establish theoretically which metal would furnish the most active catalyst. The attempted correlations based upon the electron affinity of the metal chlorides failed to give a satisfactory relationship, although this only treats the interaction as a one electron process. The mechanism of interaction may involve more than one electron, as such utilising the standard reduction potential for each complex would be a more appropriate parameter. It could then be predicted from this data that Au, specifically Au^{3+} , would be an extremely active catalyst, and this has been confirmed experimentally.¹⁸ The catalytic hydrochlorination of acetylene using carbon supported gold(III) chloride (2 mol%) and platinum(II) chloride (2 mol%) gave 85% conversion of acetylene with a selectivity of >99.9% at 61 °C.²⁰ Under similar conditions, mercury(II) chloride remains inactive, with temperature exceeding 140 °C being necessary for any significant conversion.

1.4 Relativistic effects and gold

These two examples have shown that gold can be a highly stable and exceptionally active catalyst for transformations that involve the manipulation of triple bonds, potentially implying that gold has a greater affinity for π -electron density than other transition metals.

Interest in gold catalysis has increased markedly since the 1980s, and as such research to provide explanations for the observed activity of gold has been extensively conducted. From a theoretical viewpoint, relativistic effects help to elucidate the patterns of reactivity seen for the transition metals, in particular gold.

The theoretical basis for relativistic effects comes from the joining together of quantum mechanics and special relativity.²¹ The term “relativistic effects” refers to occurrences resulting from the need to consider velocity as significant, when compared to the speed of light.²²

As the atomic nuclear charge (Z) of an atom increases, the velocity of the electrons occupying node-less orbitals increases and, as a result of relativity, their mass is also increased.²³ These relativistic effects lead to an energetic stabilisation; with the s-electrons being more tightly bound to the nucleus than if the effects were absent.²⁴ The contraction of the s-orbitals, and to a lesser extent p-orbitals, more effectively shields the nuclear charge from the remaining electrons, in particular the d- and f-electrons.²³ The consequence of this is an overall destabilisation of the d- and f-orbitals, and radial expansion.²⁵ These effects scale approximately with Z^2 , and are particularly important for elements with $Z > 72$, and are of a comparable magnitude to the shell structure effects seen for these atoms (e.g. lanthanide contraction).²⁵⁻²⁷

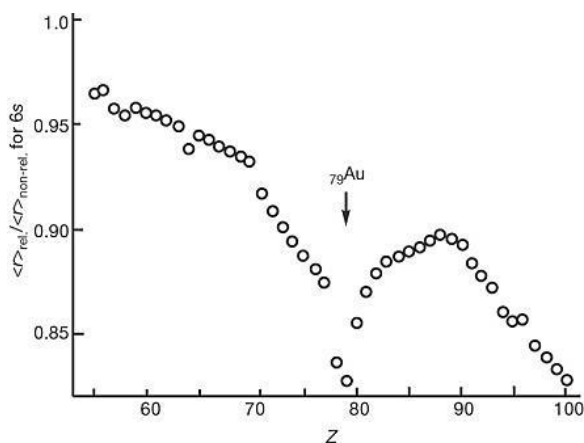


Figure 3 – Calculated relativistic contraction of the 6s orbitals of elements with $55 < Z < 100$

When the relativistic and non-relativistic radii of the 6s orbitals for elements with Z between 55 and 100 are compared there is a local minimum for Au indicating that Au

has the largest relativistic effects for elements with $Z < 100$.^{25, 26} As a consequence of this, the nonrelativistic 5d and 6s orbital energies of Au are comparable to those of the 4d and 5s orbital energies of Ag, however when relativistic effects are considered the energies differ in both the metal atoms and their hydrides, MH_2 .^{26, 28} Another consequence of relativistic effects is an associated bond-length contraction, with the Au-L bond distance being shorter than that of the corresponding Ag-L bond, with this contraction also strengthening the Au-L bond compared to Ag-L bond.^{25, 26, 28} These large relativistic effects also lower the energy of the lowest unoccupied molecular orbital (LUMO), therefore making it increasingly Lewis acidic.²² This can also be corroborated by the unusually high electronegativity of Au (2.4) when compared to Ag (1.9), where Lewis acidity generally correlates with the electronegativity of a species.²² This increase in electronegativity and Lewis acidity of Au are therefore both a direct result of the contraction of the 6s orbital due to relativistic effects.

1.4.1 Alkynophilicity

Alkynes have long been the favoured substrates in the field of homogeneous gold catalysis, due to the propensity of Au to interact strongly with the alkyne moiety. Alkynes contain two orthogonal π -orbitals, both containing two electrons, which Lewis acidic Au can interact with; both in the plane and perpendicular to the metal centre.²⁹

The coordination of the Au(I) metal centres with alkyne functionalities was investigated by Behrens *et al.* by the isolation and crystallisation of [(3,3,6,6-tetramethyl-1-thiacyclohept-4-yne)AuCl].³⁰ The complex was shown to contain an extremely strong alkyne-gold bond, with a Au-C bond length of 2.10 Å in the Au(I) complex, being of a comparable magnitude to a Au-C- σ bond (2.00 to 2.08 Å). Also the C \equiv C bond lengthened from 1.209 Å in the free alkyne, to 1.244 Å in the Au(I) complex indicating the lessening of triple bond character, again proving the existence of a strong Au-alkyne interaction.

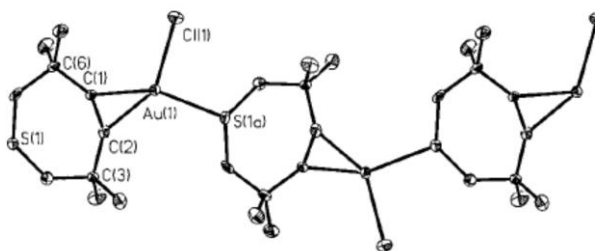


Figure 4 – Part of the polymeric chain of solid [(3,3,6,6-tetramethyl-1-thiacyclohept-4-yn)AuCl] (60% thermal ellipsoids)

As the Au(I) cation is large and diffuse it can be considered to be a “soft” Lewis acid, which will preferentially activate “soft” electrophiles, such as π -systems.²² However, when comparing the bond energies of Au(I)-ethylene and Au(I)-ethyne complexes, there is actually a 10 kcal mol⁻¹ energy stabilisation in favour of the Au(I)-ethylene complex.³¹ However, Au-alkyne complexes are more reactive than their Au-alkene counterparts; this can be attributed to the discrimination of the nucleophile in selecting between Au(I) activated electrophiles.³² When comparing the relative energies of the ethyne and ethylene LUMOs, it becomes apparent that alkynes have lower energy highest occupied molecular orbitals (HOMO) and LUMO than the corresponding alkene, in turn making them less nucleophilic and more electrophilic.³² This could therefore account for the witnessed “alkynophilicity” observed in Au catalysed transformations.

1.5 Gold catalysed transformations

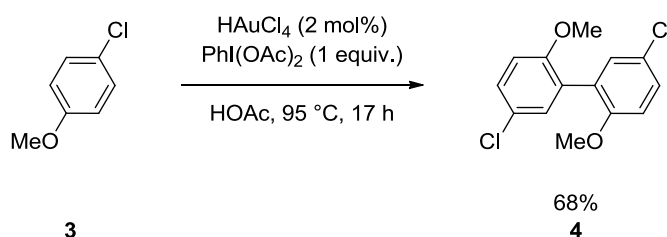
Transition metal transformations have become ubiquitous in organic synthesis; with arguably the most important class of reactions being the formation of C-C bonds, allowing for the construction of the frameworks contained within complex molecules. Although these coupling reactions have traditionally been performed by other transition metals such as palladium and nickel, gold has emerged as a catalyst that is also able to carry out these tasks. Fundamentally, there are two classes of C-C coupling reactions; homo-coupling and cross-coupling.

1.5.1 C-C bond formation

As was the case with palladium catalysis, homo-coupling was the first reported cross coupling reaction performed by gold, however this used stoichiometric quantities of gold.³³ The use of catalytic amounts of gold to promote such transformations was then investigated, however, it is important to note that after the cross-coupling has occurred Au(III) will be reduced to Au(I), needing to be re-oxidised back to the catalytic species faster than the disproportionation of Au(I) to Au(III) and Au(0).

Homocoupling

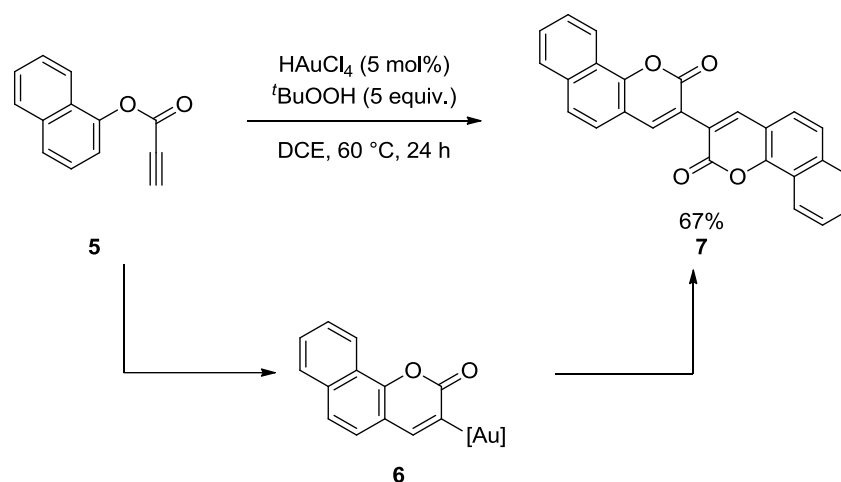
The first example of catalytic homo-coupling catalysed by gold, utilising an external oxidant to promote catalyst turnover was reported by Tse *et al.*³⁴



Scheme 1 – Gold-catalysed homocoupling of 1-chloro-4-methoxybenzene **3**

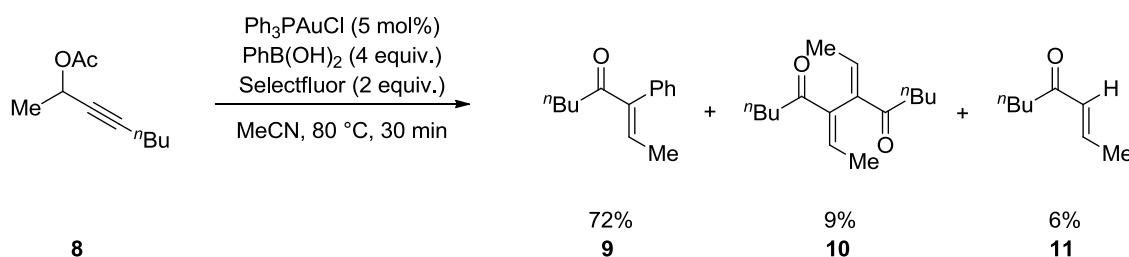
This homo-coupling of arenes demonstrates that gold is capable of inserting into Ar-H bonds and reductively eliminating to furnish symmetrical biaryl **4**, and that the use of phenyliodonium diacetate, a hypervalent iodine reagent, is sufficient for the reoxidation of Au(I) to Au(III).

Following the success of this reaction, a domino cyclisation/oxidative coupling reaction was reported by Wegner *et al.*³⁵

Scheme 2 - Tandem cyclisation and homocoupling of naphthalen-1-yl propiolate **5**

After the initial Au-catalysed activation of the alkyne moiety, cyclisation and subsequent re-aromatisation occurs. Before protodeauration of **6** can occur, the auroated intermediate is capable of catalysing the cyclisation of a second molecule of **5**. After oxidative coupling to furnish **7**, Au(I) is then reoxidised to Au(III) by the peroxide to allow catalytic turnover.

It is possible to intercept the auroated intermediate with alternate coupling partners to avoid dimer formation, and to allow further product elaboration.

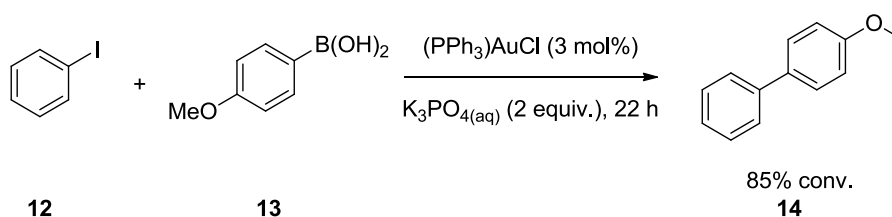
Scheme 3 – Tandem acyl transfer and coupling of oct-3-yn-2-yl acetate, **8**

Although **9** is the main product, post rearrangement dimerisation and protodeauration products are still present, although as the minor reaction products.³⁶

Suzuki cross coupling

Another important transition metal catalysed transformation is the coupling of an aryl halide and an organo-boron reagent, the Suzuki reaction.³⁷ The transition metal usually

utilised for this reaction is Pd(0) which has a d^{10} electron configuration, therefore Au(I), also d^{10} could also potentially catalyse Suzuki cross-couplings.



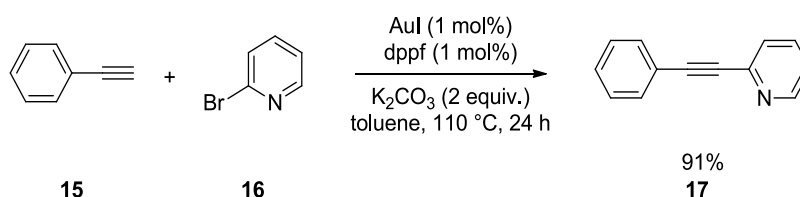
Scheme 4 – Gold-catalysed Suzuki cross coupling

Under Au(I) catalysed conditions, the cross-coupled product **14** is formed with good conversion and 100% selectivity, and has similar activity and selectivity to analogous palladium catalysts.³⁸ However, González-Arellano *et al.* have shown that when Au(III) is used under the same conditions, homo-coupling is the only product.³⁹ This dichotomy of products isolated from Au(I) and Au(III) catalysis of the same reaction is common and will be explored in later sections.

Sonogashira cross coupling

Another key transition metal catalysed reaction is the Sonogashira reaction, the coupling of vinyl or aryl halides with terminal alkynes using a palladium catalyst, a copper(I) co-catalyst and an amine base.⁴⁰

Following the success of replacing palladium with gold in the Suzuki cross-coupling, Wang *et al.* believed it would be possible to conduct a copper-free Sonogashira cross-coupling utilising gold catalysis.⁴¹ Au(I) has the same d^{10} electronic configuration as Cu(I) and is capable of interacting with alkynes in the required manner, therefore it could carry out the jobs of both palladium and copper.^{41,42}



Scheme 5- Sonogashira cross coupling of phenyl acetylene **15** and 2-bromopyridine **16**

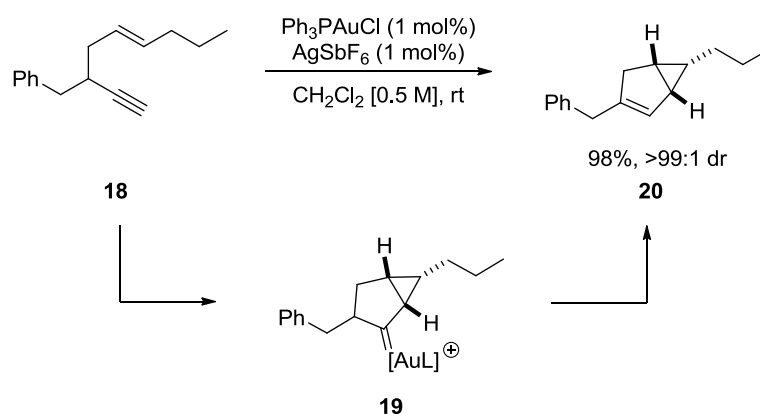
Whilst conducting experiments to determine the mechanism of the Au-promoted cross-coupling, Echavarren *et al.* found that $[\text{AuX}(\text{PPh}_3)]$ could not oxidatively insert into a number of Ar-X bonds.⁴³ As such, the claims of the ability of gold to conduct palladium-free Sonogashira couplings were rejected, with trace palladium impurities being responsible for the cross-couplings. However, González-Arellano *et al.* have carried out gold-catalysed Sonogashira reactions utilising both gold nanoparticles and Au(I) Schiff base complexes and have demonstrated that palladium is not in fact needed for the cross-coupling in those cases.⁴⁴

Gold has also been found to be an efficient transmetalation catalyst in palladium promoted Sonogashira cross-coupling reactions, with many benefits over copper(I) iodide, such as; cleaner reaction profiles and the ability to use technical grade solvents without the exclusion of air.^{45, 46}

Enyne cyclisation

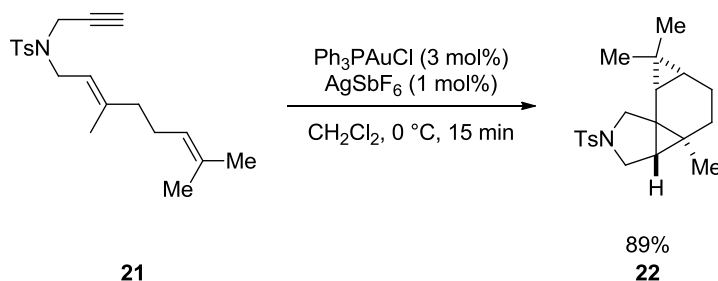
The transition metal catalysed isomerisation and rearrangement of unsaturated systems allow for the formation of structural elements not accessible through thermally promoted reactions. The cyclisation of enynes by transition metals allow for the rapid construction of numerous carbo- and heterocycles from linear substrates.

Toste *et al.* hypothesised that transition metal-alkyne complexes could be electrophilic enough to react with simple alkenes, however it was found that only a cationic Au(I) complex was the able to perform the cyclisation of 1,5 enynes.⁴⁷



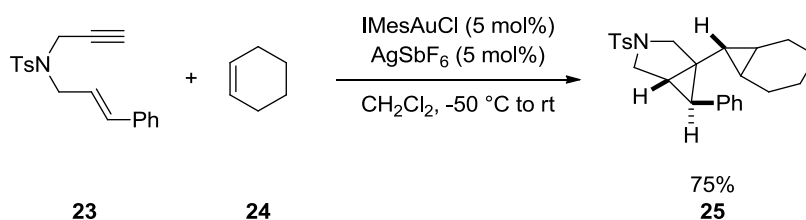
Scheme 6 – Cyclisation of 1,5 enyne 18

It has been hypothesised that enyne cyclisations proceed via a Au(I)-carbene intermediate of type **19**, which can subsequently be trapped with olefins (Scheme 7 and 8) to build up increased molecular complexity in the product.⁴⁷⁻⁴⁹



Scheme 7 – Enyne cyclisation followed by olefin trapping

Following the 5-*exo*-dig of **21**, a second cyclisation can occur to construct the tetracycle **22** as a single isomer.⁴⁹ It is also possible to utilise external olefinic nucleophiles to further expand the scope of these transformations.⁴⁸



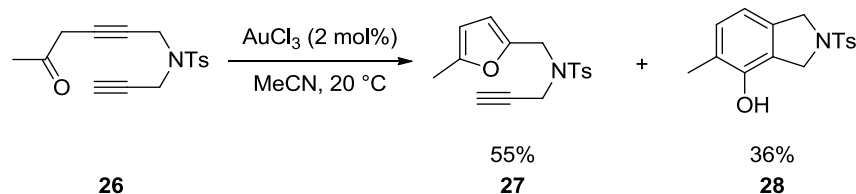
Scheme 8 – Enyne cyclisation with cyclohexene **24** incorporation

1.5.2 C-O bond formation

Carbon-oxygen bonds are ubiquitous in nature, from simple sugars to complex natural products, as well as being present in a plethora of pharmaceutical drugs, therefore the development of novel methods for the formation of C-O bonds is of the utmost importance. Au-alkyne complexes have already been shown to be inherently electrophilic; therefore the reaction of these complexes with nucleophilic oxygen should provide an expedient route for the formation of C-O bonds.

Furan synthesis

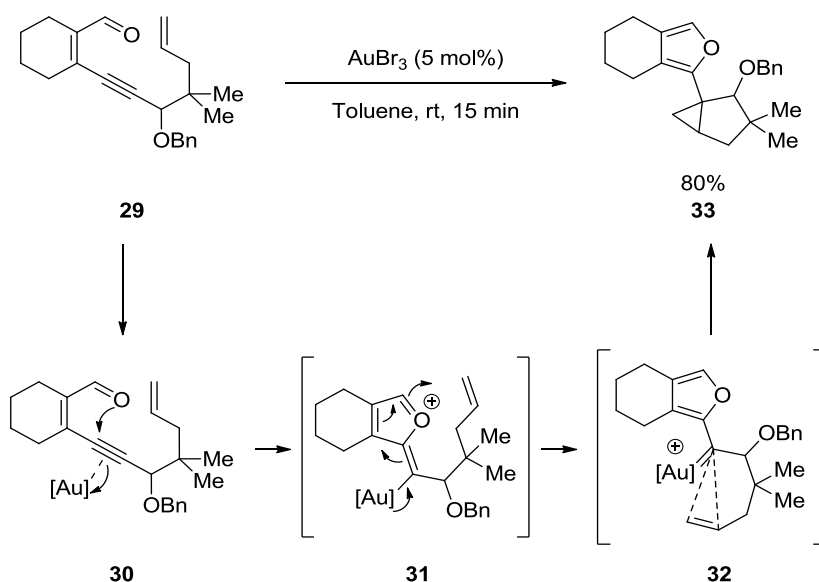
An excellent example of gold catalysed C-O bond formation was reported by Hashmi *et al.* in 2000, with an intramolecular attack of a ketone onto an alkyne.⁵⁰



Scheme 9 – Gold-catalysed furan synthesis from ketone 26

Following the attack of the ketone onto the alkyne to furnish furan **27**, AuCl₃ further catalyses a Diels-Alder cyclisation, with subsequent ring opening and re-aromatisation providing phenol **28**. Selective formation of both the furan and phenol derivatives was possible by varying the reaction time.⁵⁰

Utilising carbonyls as the nucleophilic oxygen source has subsequently been applied by many research group to synthesise a range of furan derivatives.^{51, 52}

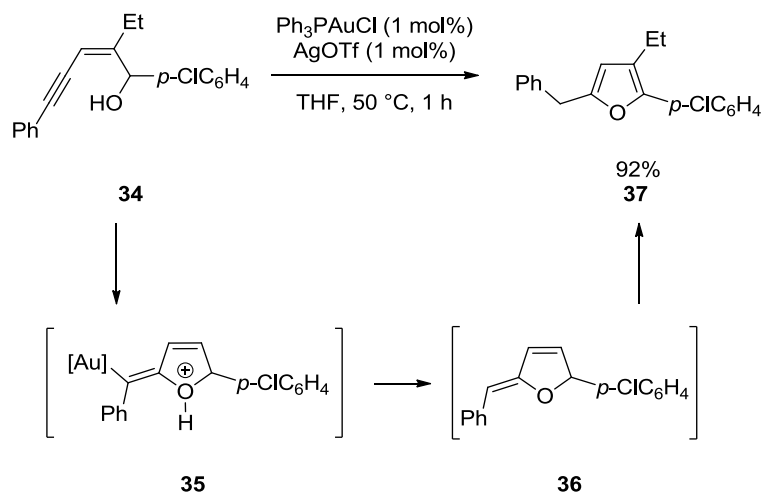


Scheme 10 – Furan formation followed by cyclopropanation of intermediate 32

Nucleophilic attack of the oxygen onto the Au-alkyne complex **30** furnishes the furan moiety, with subsequent cyclopropanation of the Au-carbenoid intermediate **32** furnishing the tricycle **33**.⁵³ A multitude of gold catalysed furan syntheses that also

include tandem cyclisations have been reported enabling multiple C-O and C-C bonds to be formed in one-pot.⁵²

Subsequent studies have shown it is possible to synthesise furan derivatives from starting materials containing a wide range of functionality, with alcohols being employed as the nucleophile in the synthesis of furans.⁵⁴⁻⁵⁶



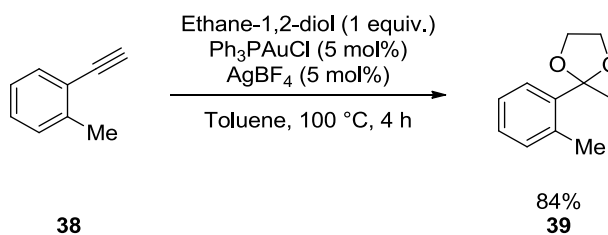
Scheme 11 – Furan synthesis from alcohol **34**

Following alkyne activation, an *anti*-5-*exo-dig* cyclisation by the hydroxyl group occurs to afford the aurophilic intermediate **35**. Proto-deauration regenerates the catalytic species, and double bond isomerisation of **36** affords the furan product **37**.⁵⁷

Epoxides have also been used as the nucleophilic oxygen source in numerous syntheses, however mechanistic insights have shown that epoxide opening precedes cyclisation.⁵⁸

Acetal Formation

External oxygen sources can also be utilised in gold-promoted nucleophilic addition reactions. Santos *et al.* have demonstrated the regioselective formation of cyclic acetals from terminal alkynes.⁵⁹

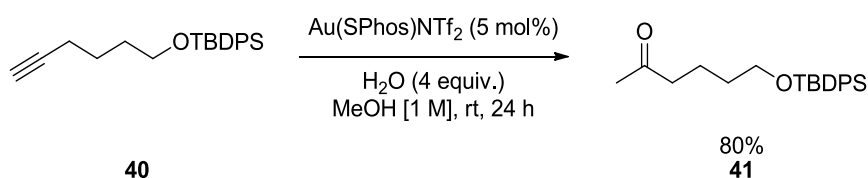


Scheme 12 – Acetal formation by nucleophilic addition of ethane-1,2-diol to alkyne 38

After the initial alcohol addition to the activated alkyne and proto-deauration, an enol ether intermediate is formed, however a rapid isomerisation to the more stable acetal **39** occurs. The addition of the diol occurs exclusively at the most sterically encumbered carbon atom of the alkyne to give the cyclic acetal **39**.

Ketones by alkyne hydration

Previous methods for the hydration of alkynes have employed the use of mercury salts ($\text{HgO-H}_2\text{SO}_4/\text{HgO-BF}_3$), however, alternative methods have been sought to eliminate the use of these toxic complexes. Unfortunately, the catalytic systems developed, along with the HgO complexes, require the use of acidic additives, high temperatures or both. Corma *et al.* have shown that cationic gold(I) is capable of affecting the hydration of alkynes at ambient temperature and without the need for acidic additives.⁶⁰

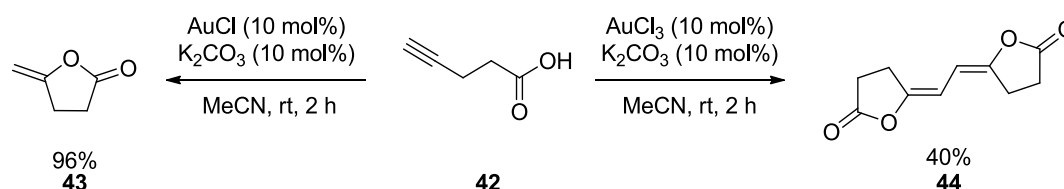


Scheme 13 – Regioselective gold-catalysed alkyne hydration

Dimethyl ketals are formed as intermediates in this transformation as the addition of MeOH to the alkyne is faster than H_2O (as determined by ^1H NMR), with subsequent hydrolysis providing the ketone **41**. The absence of acidic promoters within this reaction allows for the inclusion of acid-labile functional groups in the substrates.

Lactone formation

Whilst investigating the formation of alkylidene lactones from the corresponding acetylenic acids, Pale *et al.* discovered an interesting dichotomy between the Au(I) and the Au(III) catalysed reactions.⁶¹

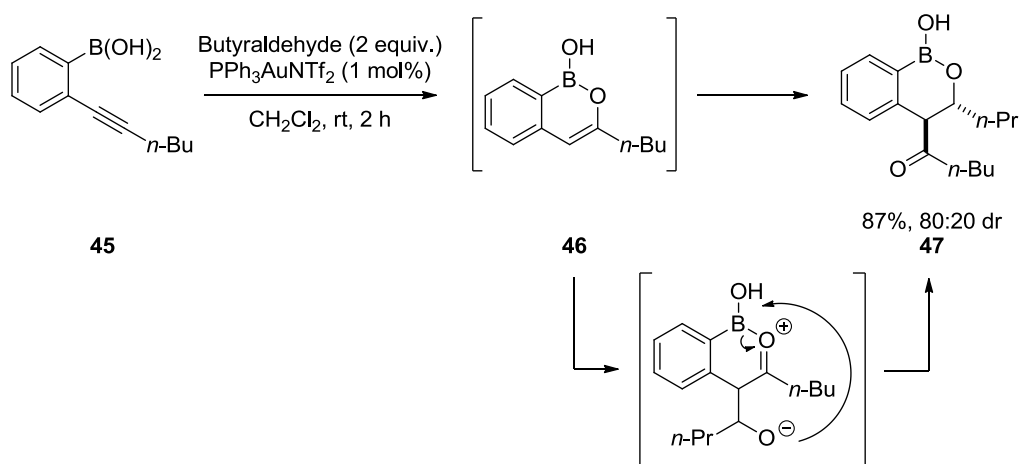


Scheme 14 – Contrasting reactivity of pent-4-ynoic acid **42** under gold(I) and gold(III) catalysis

The use of Au(I) chloride gave the expected 5-*exo-dig* product **43**, however Au(III) chloride provides the dimerised product **44**, although in modest yield. As shown previously, Au(III) was capable of catalysing the dimerisation of α,β -unsaturated ketone **5**, although an external oxidant was necessary to promote catalyst turnover, which may explain the poor yield for this reaction.

Boron enolate formation

Sheppard *et al.* have shown it is possible to synthesise a range of boron enolates from the corresponding *o*-alkynylbenzene boronic acids under mild, gold-catalysed conditions.⁶²

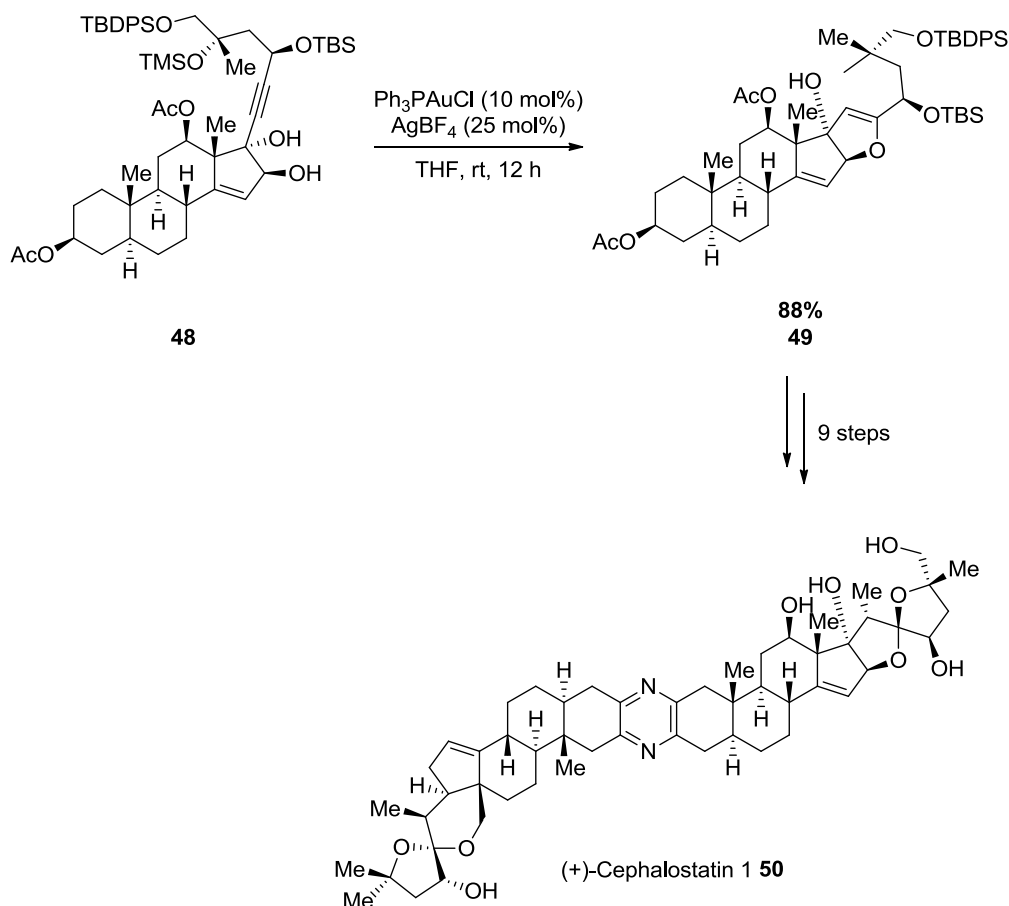


Scheme 15 – Boron enolate formation and subsequent diastereoselective aldol reaction

Following the gold-catalysed formation of boron enolate **46**, which is isolable, the aldol reaction with butyraldehyde occurs, with subsequent rearrangement, to give **47** in excellent yield and good diastereoselectivity. The synthetic utility of this reaction was demonstrated by the further functionalisation of the aldol products by oxidation, Suzuki or Chan-Lam couplings.

1.5.3 Gold catalysed C-O bond formation in total synthesis

Fortner *et al.* have taken advantage of gold's ability to activate alkynes to nucleophilic attack by hydroxyl groups during the synthesis of the eastern half of (+)-cephalostatin **50**, a potential anti-cancer agent.⁶³



Scheme 16 – Late-stage gold-catalysed cyclisation *en route* to (+)-cephalostatin **50**

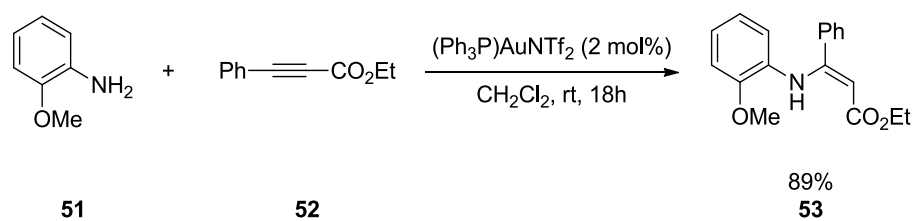
The use of the Au(I)-catalysed 5-*endo-dig* cyclisation, towards the end of a complex total synthesis, onto a highly substituted internal alkyne demonstrates the power of gold catalysis.

1.5.4 C-N bond formation

Another important class of carbon-heteroatom bond is that with nitrogen, being ubiquitous in nature and biologically active molecules. Novel methods for the introduction of a wide range of nitrogen containing functional groups are therefore desirable, especially under non-forcing conditions. Having demonstrated the ability of gold to catalyse the nucleophilic addition of heteroatoms to alkynes, it follows that nucleophilic nitrogen can also be employed.

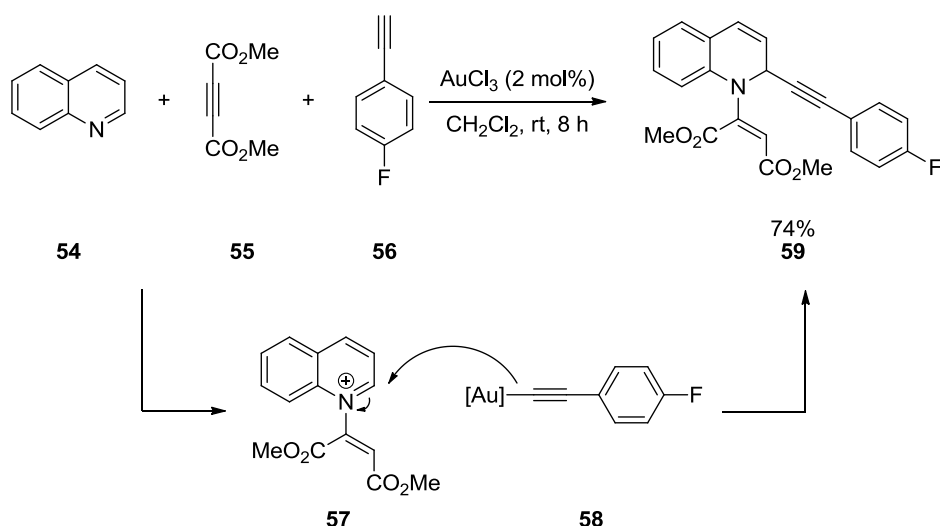
Hydroamination of alkynes

With analogous reactivity to the C-O bond forming reactions, it is possible to promote the nucleophilic addition of nitrogen to an alkyne.



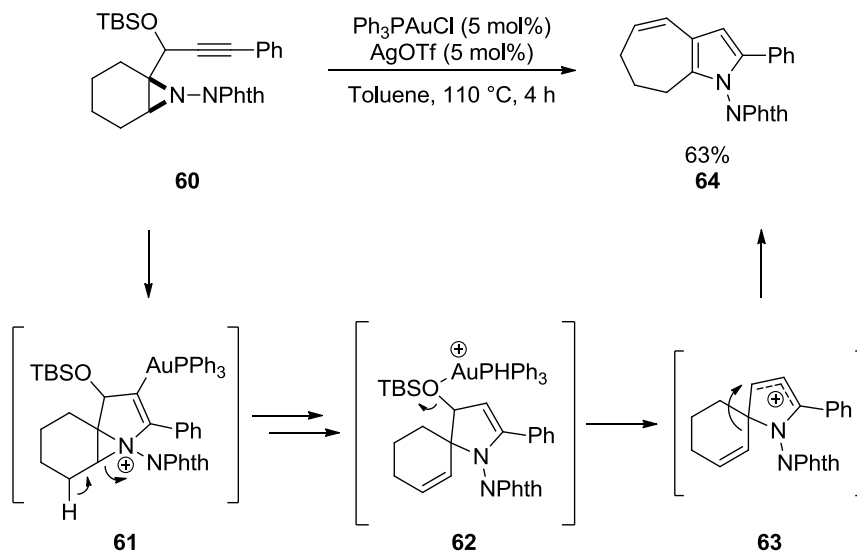
Scheme 17 – Formation of enamine **53** by hydroamination of **52** with 2-methoxyaniline **51**

This reaction affords *N*-arylimine **53** as a single regioisomer under mild conditions, with control experiments ruling out a simple Michael addition of the aniline **51** to the alkyne **52**.⁶⁴ Further examples building up increased molecular complexity via tandem reaction have also been reported.⁶⁵

Scheme 18 – Hydroamination of dimethyl but-2-ynedioate **55** followed by gold-acetylide addition

After the initial hydroamination of **55** by quinolone **54**, the iminium intermediate **57** reacts with the terminal alkyne, as the Au-acetylide **58**, to give the enamine **59**. This reaction highlights the ability of gold to perform two catalytic roles within the same reaction.

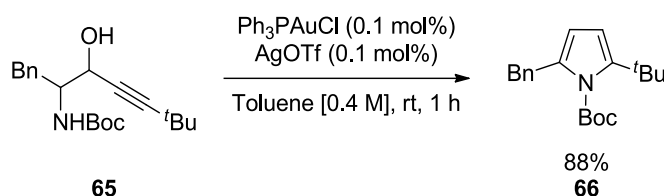
Pyrrole formation

Scheme 19- Pyrrole formation by 5-endo-dig cyclisation of aziridine **60**

As with the furan syntheses utilising nucleophilic oxygen, nitrogen heterocycles can also be formed using Au-catalysis. A number of routes have been devised however two

general strategies are employed for pyrrole formation; aziridine opening and the intramolecular cyclisation of 1-amino-3-alkyn-2-ols.^{55, 56, 66, 67} After the familiar *5-endo-dig* cyclisation of the aziridine **60** with the Au(I)-activated alkyne, the ammonium cation is quenched by β -hydride elimination and aziridine ring-opening to give spirocyclic intermediate **62**. Subsequent Au(I)-catalysed ionisation provides an allylic cation which undergoes Wagner-Meerwein rearrangement/ring expansion to furnish the pyrrole **64** after proto-deauration and re-aromatisation.⁶⁶

An alternative method for the gold promoted synthesis on pyrroles employs the use of 1-amino-3-alkyn-2-ols.⁵⁶

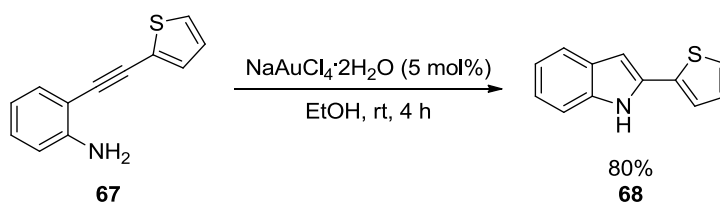


Scheme 20 – Synthesis of pyrrole **66** from 1-amino-3-alkyn-2-ol **65**

The hydroxyl group is necessary for re-aromatisation following cyclisation and proto-deauration of **65**; with this scaffold being used in alternative syntheses of pyrrole.⁵⁵

Indole formation

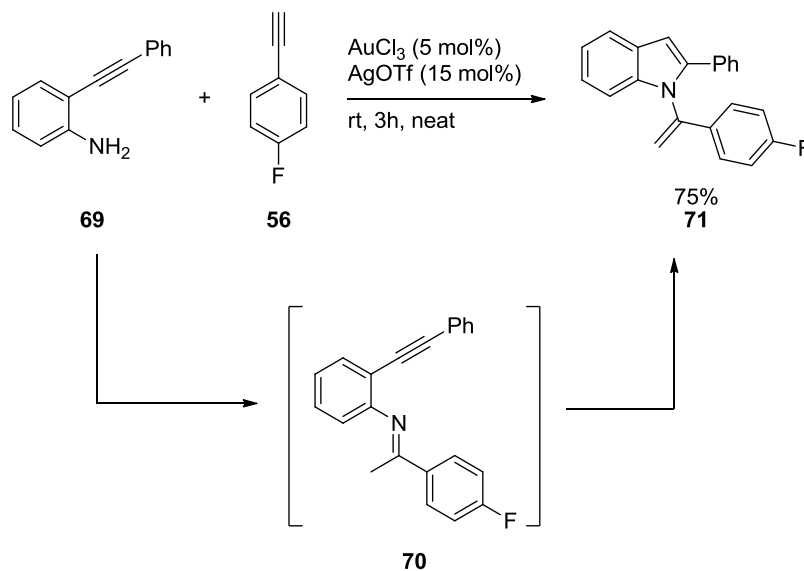
Another nitrogen-containing heterocycle that has been synthesised utilising Au-catalysis is indole. Arcadi *et al.* reported the first general synthesis of indole from *o*-alkynylanilines using sodium tetrachloroaurate(III) dihydrate as the catalyst.⁶⁸



Scheme 21 – Arcadi's indole synthesis

Previous examples of Au-promoted indole formation require electron withdrawing groups on the nitrogen atom to successfully promote the reaction, with extremely forcing conditions needing to be employed to encourage catalyst turnover when no

electron withdrawing groups are present.⁶⁹ Subsequent research has shown that it is possible to carry out tandem processes to increase complexity in the reaction products, with Li *et al.* synthesising *N*-vinylindoles in one-pot *via* the double hydroamination of *o*-alkynylanilines with terminal alkynes.⁷⁰



Scheme 22 – Double hydroamination of alkynes *en route* to indole **71**

After initial activation of the terminal alkyne **56** by gold(III) triflate, formed *in situ* from gold(III) chloride and silver(I) triflate, the first hydroamination provides imine **70**, with the second hydroamination furnishing the *N*-vinylindole **71**.

1.6 Indole

Indole **72**, the trivial name for benzopyrrole, comes from the combination of *indigo* and *oleum*, as a result of the aromatic compounds' isolation from natural indigo dye.⁷¹

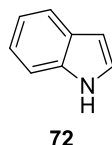


Figure 5- Indole, **72**

Since its isolation, indole has become a privileged structure, a term first used by Evans *et. al.* in 1988, and is defined as “a single molecular framework able to provide ligands for diverse receptors”.⁷² As such, indole scaffolds have been utilised in a wide range of applications including fragrances, agrochemicals, pigments, material science, as well as being a key motif in a wide range of natural products.⁷³ Due to its high affinity for a wide range of receptors, the [5,6] bicyclic framework of indole has also been exploited extensively in the field of medicinal chemistry.

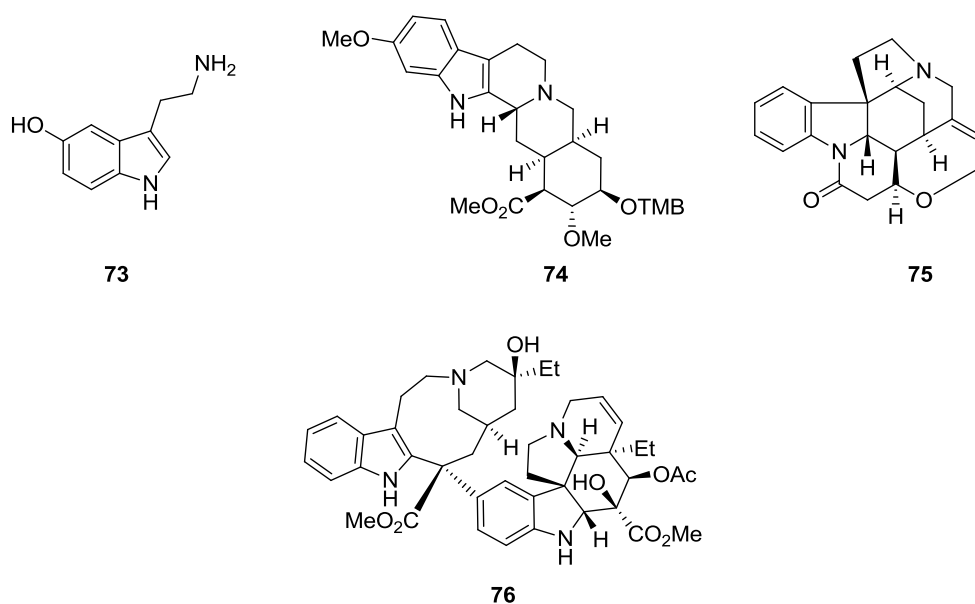


Figure 6 – Serotonin **73**, Reserpine **74**, Strychnine **75** and Vinblastine **76** containing the privileged indole nucleus

Serotonin **73**, also known as 5-hydroxytryptamine (5-HT), is a neurotransmitter which plays a variety of roles in physiology including cardiovascular function, sensory

perception and behaviour and is one of the oldest signalling molecules, being found throughout history.⁷⁴ Reserpine **74**, a lipid-soluble indole alkaloid, first isolated from India snake root *R. serpentine* Benth in 1952, is a potent central nervous system depressant.⁷⁵ Reserpine was introduced as one of the first drugs for the treatment of anxiety and mental disorders, and it is still used today.⁷⁶ Strychnine **75** is an extremely complex natural product, having 7 fused rings and 6 contiguous stereocenters. It is also a well-known poison (~50 mg is lethal for an adult human), which blocks postsynaptic inhibition in the spinal cord by antagonising the transmitter glycine.⁷⁷ Vinblastine **76**, isolated from *Catharanthus roseus*,⁷⁸ acts as a potent chemotherapeutic agent by inhibiting cell mitosis.⁷⁹ It is particularly interesting as it contains both an indole and an indoline motif.

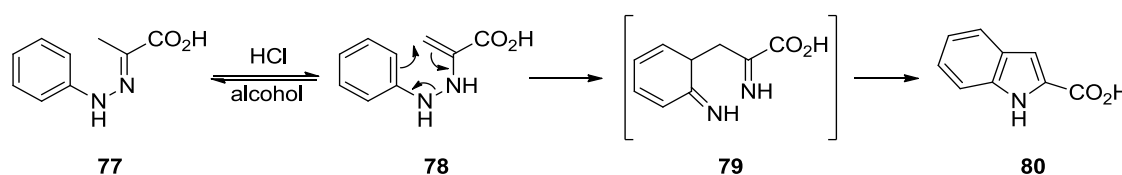
Due to the range of pharmacological efficacy of indole containing alkaloids, significant effort has gone into devising *de novo* syntheses of these molecules, which allow for the formation of analogues by subtle structural modification.

1.6.1 Indole synthesis

Considering the pharmaceutical importance of the indole nucleus and its derivatives it is not surprising that methods which allow for the rapid formation of indoles with varied functionality have garnered considerable attention. Some of the most popular are described below.

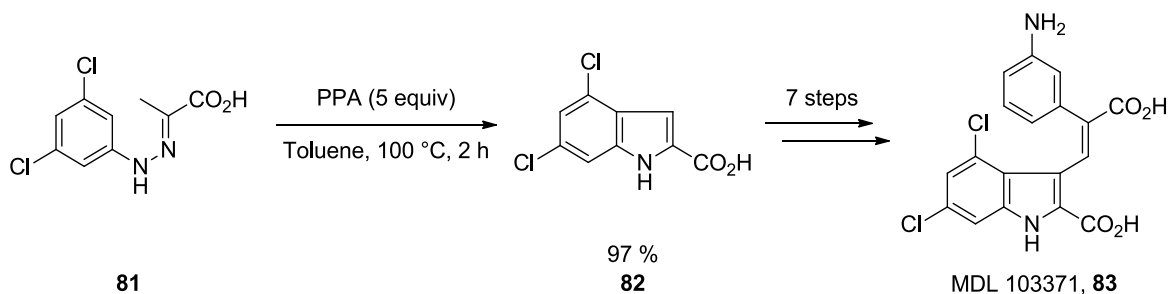
Fischer indole synthesis

What is now known as the Fischer indole synthesis was first reported in 1883, by the treatment of (*E*)-2-(2-phenylhydrazono)propanoic acid **77** with alcoholic hydrogen chloride.⁸⁰



Scheme 23 – First example of the Fischer indole synthesis

Since then many variants of the synthesis have been reported, utilising Lewis and Brønsted acids, as well as thermal and microwave promoted cyclisations.

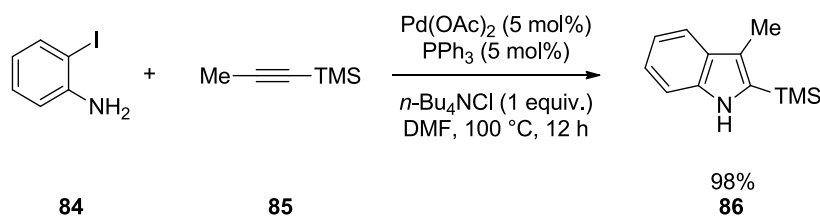


Scheme 24 – Fischer indole synthesis *en route* to MDL 103371, 83

Watson *et al.* reported a polyphosphoric acid mediated fischer indole protocol on route to the synthesis of MDL 103371, a potential treatment of stroke. The power of this transformation is highlighted by the ability to perform this reaction on multi-kilogram scale.⁸¹

Larock indole synthesis

An alternative synthesis of indole was reported by Larock in 1991, utilising palladium catalysis to affect the heteroannulation of internal alkynes by *o*-iodoaniline **84**.⁸²



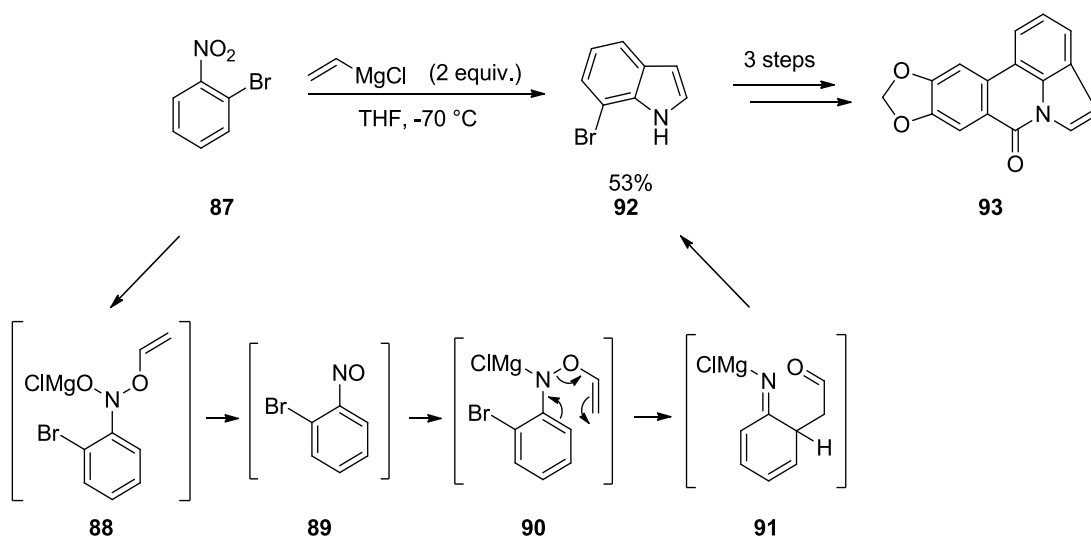
Scheme 25 – Larock indole synthesis

This reaction proceeds *via* regioselective *syn*-insertion into the alkyne, ligand displacement by the aryl nitrogen atom and reductive elimination to furnish the desired indole derivative **86**. Due to the simplicity of this reaction and its functional group tolerance this method has also been applied to the synthesis of many indole derivatives, azaindoles,⁸³ quinolones⁸⁴ and tetrahydroindoles.⁸⁵

Bartoli indole synthesis

Another novel method for the preparation of indoles was reported by Bartoli *et al.* which features a [3,3]-sigmatropic rearrangement analogous to the Fischer indolisation

step.⁸⁶ This method has been used to synthesise 7-bromoindole **92** as part of the concise synthesis of hippadine **93**, which reversibly inhibits fertility in male rats.⁸⁷

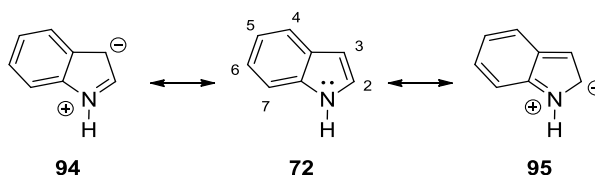


Scheme 26 – Bartoli indole synthesis towards the synthesis of hippadine **93**

The indole syntheses shown thus far all benefit from their generality, as well as the commercial availability of the starting materials involved, allowing for the synthesis of diverse indole frameworks.

1.7 Reactions of Indole

Indole is an electron-rich aromatic, with the non-bonding nitrogen lone pair overlapping with the conjugated π -system, allowing for alternate resonance structures.

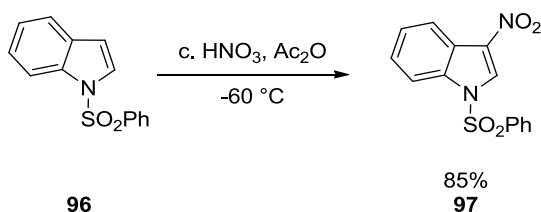


Scheme 27 – Indole resonance structures

Of the many resonance structures available to indole, the most important are **94** and **95**, which place the negative charge on the C-3 and C-2 carbons respectively. The thermodynamically favoured resonance structure is **94** due to the retention of benzenoid character of the bicycle, with **95** having perturbed this system. These qualitative

observations are further supported by the NMR spectrum of indole, with the C-3 proton being the most shielded, as well as frontier electron density calculations.⁸⁸ As such, derivitisation of indole is commonly achieved through electrophilic aromatic substitution at the C-3 position, which is $\sim 10^{13}$ times more reactive than benzene.⁸⁹

Classical electrophilic aromatic substitution, usually seen for benzene and its derivatives can also be employed in the reaction of indole.

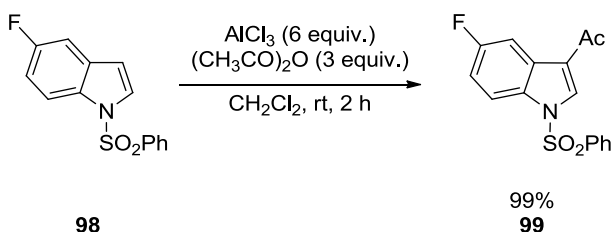


Scheme 28 – C-3 nitration of 1-(phenylsulfonyl) indole 96

Although the direct nitration of indole proceeds poorly,⁹⁰ Gribble *et al.* have shown that *N*-protection with electron withdrawing groups facilitates nitration under reasonable conditions.⁹¹ It is worth noting that under traditional nitration conditions inextractable products were formed, potentially due to the acid-catalysed polymerisation of indole.⁹²

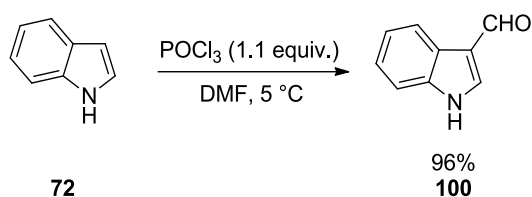
Friedel-Crafts

The Friedel-Crafts reaction is one of the most important C-C bond forming reactions in organic chemistry, with Friedel-Crafts acylations allowing for the formation of aryl ketones.⁹³ Due to the inherent reactivity of indole, attempted acylations using acetic anhydride in acetic acid gave mainly 1,3-diacetylindole,⁹⁴ however Gribble *et al.* were able to perform the regioselective acylation of *N*-protected indoles.⁹⁵



Scheme 29 – C-3 Acylation of 5-fluoro-1-(phenylsulfonyl) indole 98

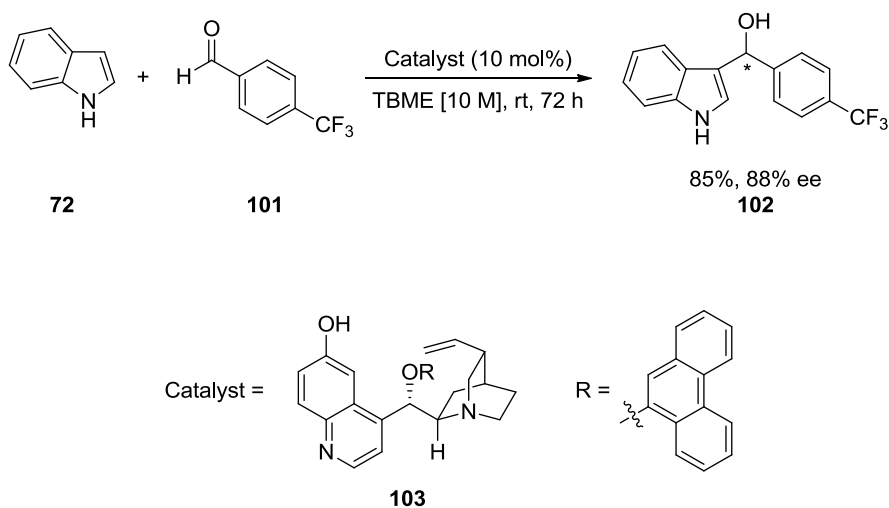
An alternative method for the addition of carbonyl functionality at the C-3 position is the Vilsmeier reaction.⁹⁶



Scheme 30 – C-3 formylation of indole **72** by Vilsmeier reaction

This reaction is the most efficient route for the formation of 3-formylindoles, and can even be used on indoles bearing an electron-withdrawing group at the C-2 position.⁹⁷ Dimethylformamide can also be replaced by tertiary amides of other acids to give alternative 3-acyl indoles.⁹⁸

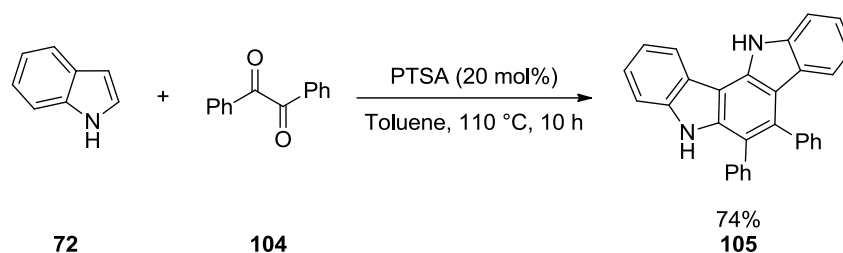
Deng *et al.* have described the enantioselective Friedel-Crafts reaction of indoles with aldehydes catalysed by bi-functional cinchona alkaloid **103**.⁹⁹



Scheme 31 – Friedel-Crafts reaction of indole **72** and aldehyde **101**

This reaction is applicable to a wide range of indoles and aldehydes, as well as α -ketoesters. Previous attempts to install hydroxyl groups chirally using metal catalysts only provided high enantioselectivities for the nucleophilic addition of indole to ethyl 3,3,3-trifluoropyruvate, with other carbonyl additions being unsuccessful.¹⁰⁰

Nair *et al.* have developed the formal double Friedel-Crafts reaction of indole **72** and diaryl-1,2-diones to afford indolo[3,2-*a*]carbazoles.¹⁰¹

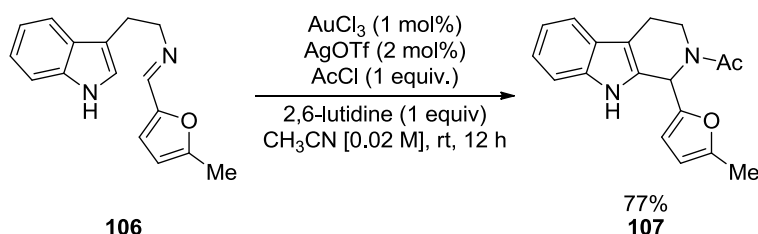


Scheme 32 – Double Friedel-Crafts alkylation of indole **72** by benzil **104**

The indolocarbazole framework has many of the biological properties of indolyl analogues, such as antitumor, antimicrobial and antihistaminic activity, but also shows intense luminescent properties for potential application in organic LEDs.¹⁰²

Pictet-Spengler

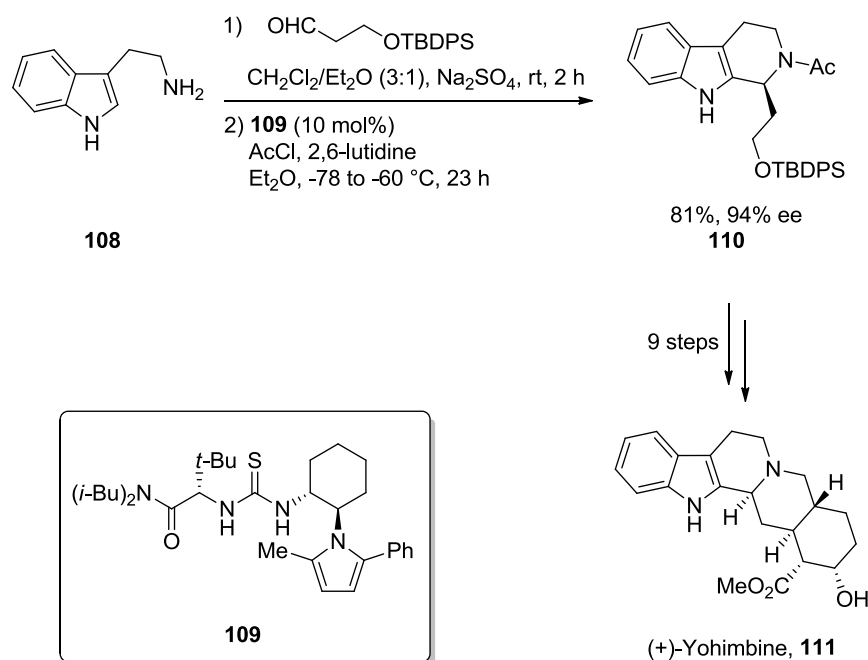
The Pictet-Spengler reaction has been utilised extensively in the synthesis of indole- and isoquinoline-alkaloids,¹⁰³ predominately using strong Brønsted acids to promote the cyclisation of an electron-rich aromatic onto an imine.¹⁰⁴



Scheme 33 – Gold-catalysed Pictet-Spengler reaction

Youn has shown it is possible to use gold(III) chloride and silver(I) triflate to catalyse the cyclisation of indole onto imines under mild conditions to afford tetrahydro- β -carboline.¹⁰⁵ It is worth noting that in this case, acylation of the imine was required to enhance reactivity.

Jacobsen *et al.* have shown it is possible to carry out the Pictet-Spengler reaction of indole **108** enantioselectively in the total synthesis of (+)-yohimbine **111**, a monoterpene alkaloid with diverse biological activity.¹⁰⁶

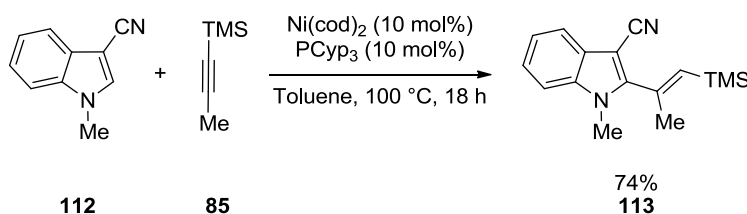


Scheme 34 – Enantioselective Pictet-Spengler reaction en route to (+)-yohimbine 111

The chirality installed in the Pictet-Spengler cyclisation is the template for a highly diastereoselective intramolecular Diels-Alder reaction towards the end of the total synthesis.

Alkyne addition

As well as the addition to electron-deficient systems such as carbonyls and imines, it is also possible to promote indoles addition to carbon electrophiles. Nakao and Hiyama *et al.* have carried out the hydroheteroarylation of unactivated alkynes by nickel-catalysed Ar-H activation.¹⁰⁷

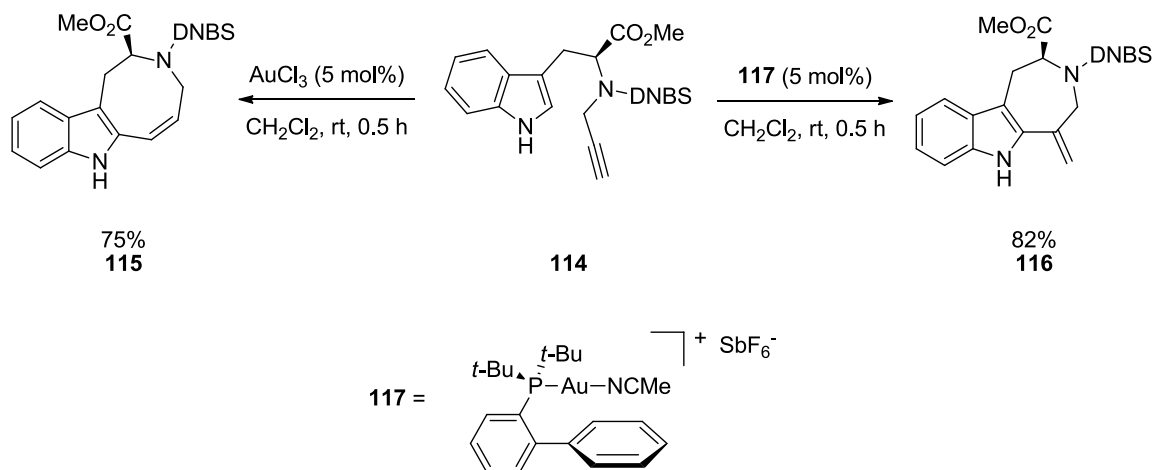


Scheme 35 – Nickel catalysed hydroheteroarylation of trimethyl(prop-1-yn-1-yl)silane 85

This methodology has also been applied to a range of heteroaromatics, giving regioselective hydroarylation products, however if trimethylphosphine is used as the

ligand in this reaction, the product of arylocyanation of the alkyne is the major product.¹⁰⁸

It is also possible to achieve intramolecular hydroarylation of alkynes by indole, with Echavarren *et al.* utilising Au(I) and Au(III) catalysts to effect complimentary cyclisations.¹⁰⁹

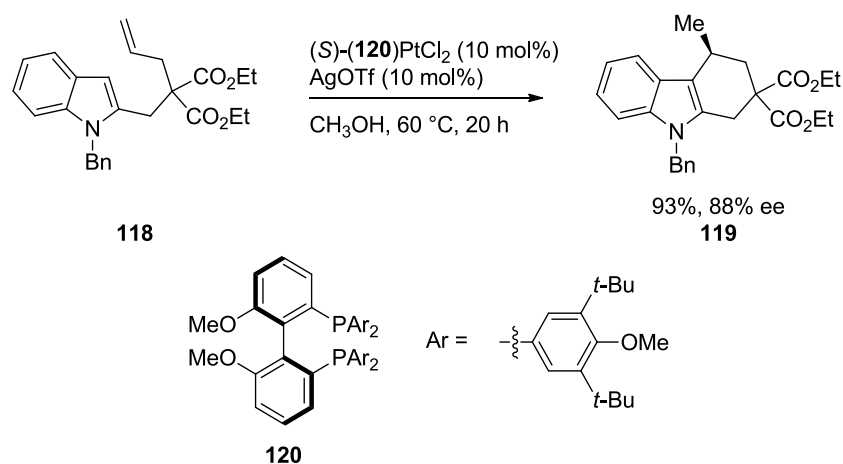


Scheme 36 – Divergent gold(III)- and gold(I)-catalysed synthesis of tricycle **115** and **116**

In this divergent transformation, cationic Au(I) complex **117** facilitates a 7-*exo*-dig cyclisation, whereas Au(I) chloride provides indoloazocines through a rare 8-*endo*-dig pathway.

Alkene addition

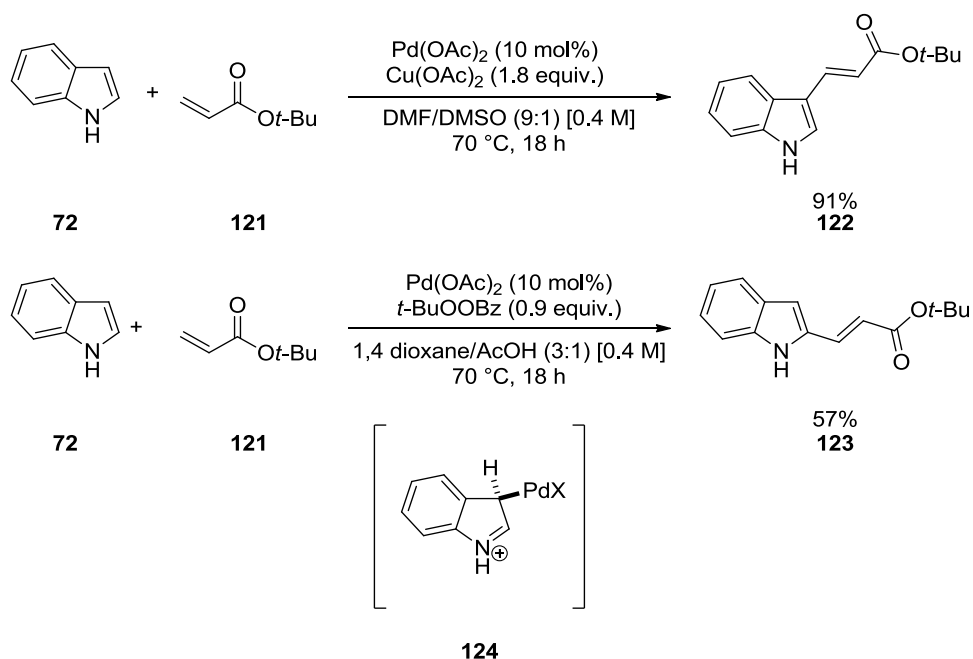
Analogous to the reaction of alkynes, the nucleophilic addition of indoles to unfunctionalised alkenes has only recently received significant interest. Platinum complexes have shown to be successful for this, with the stability of the platinum(II) intermediates allowing for protonation as the final step of the catalytic cycle.¹¹⁰



Scheme 37 – Platinum-catalysed intramolecular alkene addition of indole 118

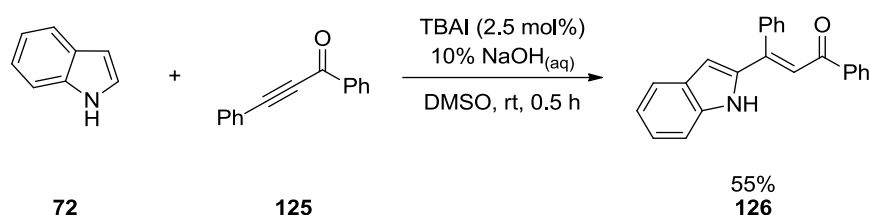
A range of protected indole derivatives successfully underwent the 6-exo-trig cyclisation, whilst unprotected indole have drastically reduced enantiomeric excesses.¹¹¹

Hydroarylation of indole is also possible using palladium(II) complexes, however due to the inherent instability of the σ -alkyl-palladium(II) species, unsaturated products are isolated through β -hydride elimination from these intermediates.

Scheme 38 – Nucleophilic addition of indole 72 to *tert*-butyl acrylate 121 at both C-3 and C-2 position

Although both reactions are believed to go through the same reactive intermediate, **124**; in polar solvents alkenylation of indole at C-3 was observed, following rearomatisation and Heck-type reaction. In contrast, under protic reaction conditions, charge stabilisation of intermediate **124** allows for the migration of the C-3-PdX bond to the highly activated 2-position of the iminium intermediate, giving rise to the C2-alkenylated product **123**.¹¹²

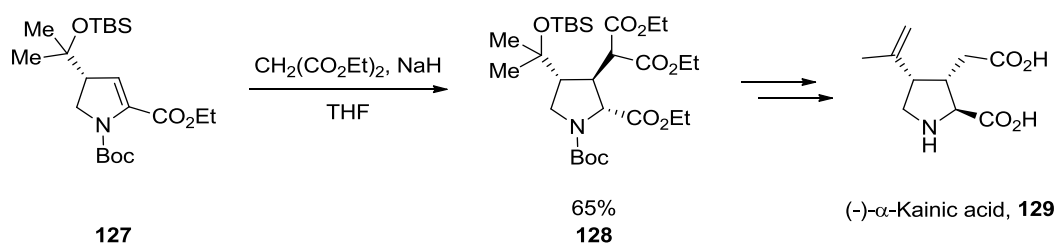
Another method for the preparation of C-2 alkenylation of indoles is the phase transfer catalysed conjugate addition to ynones.¹¹³



Scheme 39 – Conjugate addition of indole 72 to 1,3-diphenylprop-2-yn-1-one 125

Michael addition

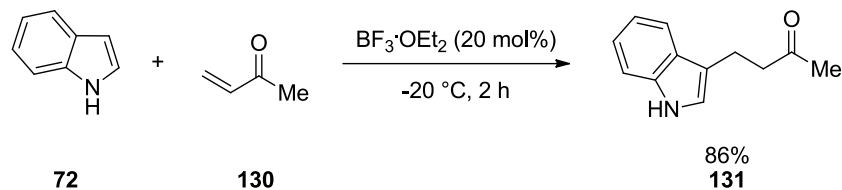
The 1,4-addition (or conjugate addition) of a carbanion, or other nucleophile, to activated olefins such as α,β -unsaturated carbonyl compounds is known as the Michael reaction. The Michael reaction is widely used in organic synthesis for its ability to rapidly construct C-C bonds.



Scheme 40 – Asymmetric Michael addition *en route* to (-)- α -kainic acid, 129.

In this example, Rubio *et al.* have affected the asymmetric Michael addition of dimethylmalonate to 2, 3-didehydroprolinate **127** towards the synthesis of kainic acid **129**.¹¹⁴

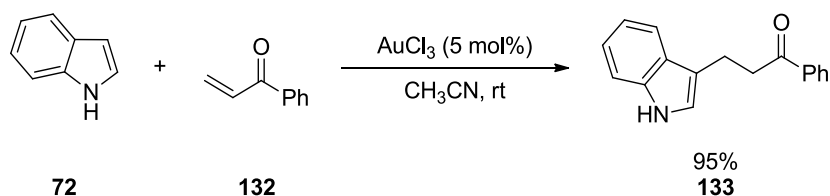
Although traditionally using activated methylene nucleophiles, such as dimethylmalonate, indole has been shown to be an excellent nucleophile in Michael additions.



Scheme 41 – Lewis acid catalysed Michael addition of indole **72** into but-3-en-2-one **130**

Although the Lewis acid catalyst allowed for the pioneering Michael addition of indole to methyl vinyl ketone **130** (MVK), the substrate scope was narrow, and mainly confined to the addition to MVK.¹¹⁵ However, Harrington and Kerr later published a general procedure for the Michael addition of indole to a variety of α,β -unsaturated carbonyl compounds using ytterbium(III) trifluoromethanesulfonate.¹¹⁶ Subsequent studies have shown that a wide array of catalysts are able to promote the Michael addition of indole to MVK, the results of which are highlighted in an excellent review by Bandini and Eichholzer.¹¹⁷

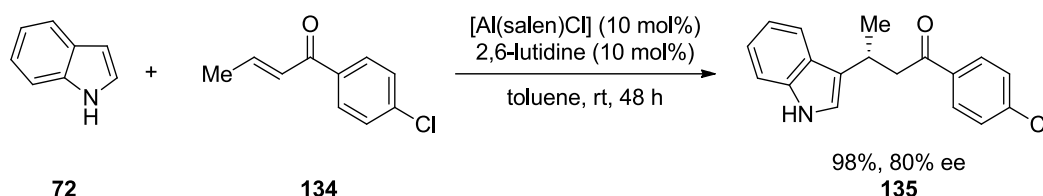
An example of particular interest was the gold(III) chloride promoted Michael addition of indole to MVK.¹¹⁸



Scheme 42 – Gold-catalysed Michael addition of indole **72** into 1-phenylprop-2-en-1-one **133**

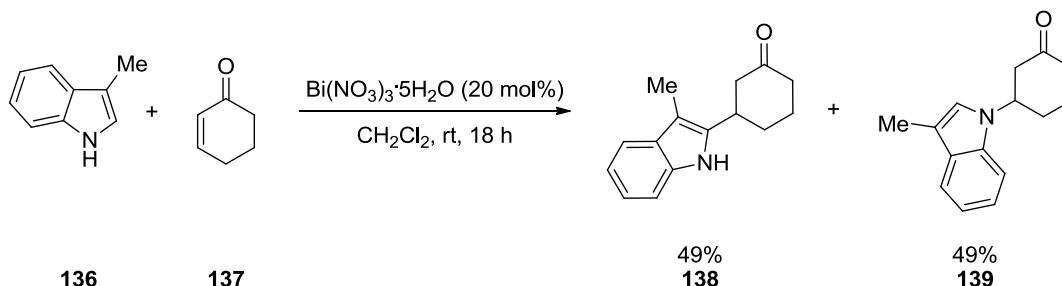
It is postulated that instead of acting as a traditional Lewis acid, the gold(III) directly attacks the C-3 position of indole, affording an arylgold(III) species as the reactive intermediate. This mechanism of action has also been proposed by Li *et al.* in their addition of pentane-2,4-dione to unactivated alkenes.¹¹⁹

The asymmetric metal-catalysed addition of indole to simple α,β -unsaturated carbonyl systems has proved difficult, however Bandini *et al.* pioneered the use of a (*R,R*)-[Al(salen)Cl] complex, in the presence of a lutidine additive, to give high enantioselectivities for the addition of indole **72** to (*E*)-1-phenylbut-2-en-1-one **134** and its derivatives.¹²⁰



Scheme 43 – Enantioselective Michael addition of indole to α,β -unsaturated ketone **134**

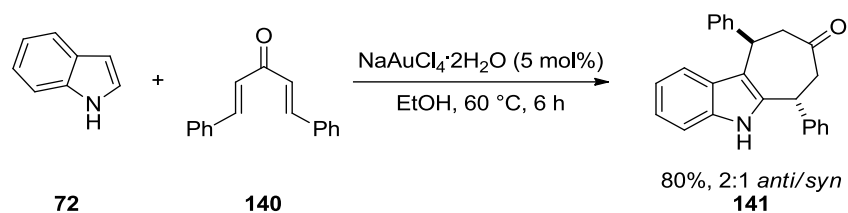
Although the vast majority of conjugate addition chemistry occurs at the more reactive C-3 position of indole, C-2 and N-1 functionalisation can become competitive if C-3 substituted indoles are involved in the reaction.¹²¹



Scheme 44 – Michael addition of indole **72** at C-2 and N-1 positions

It was noted that the C-3 substituent, as well as reaction media, greatly affect the regioselectivity of the reaction, with aprotic solvents favouring *N*-adducts, and protic solvents increasing the percentage of C-2 adduct formed, however a general tendency towards *N*-substitution is maintained.

It has previously been demonstrated by Arcadi *et al.* that indole is capable of undergoing double conjugate addition with DBA **140**.¹²²



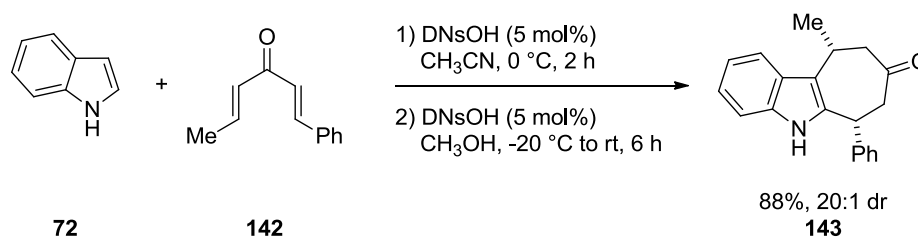
Scheme 45 – Arcadi's double alkylation of indole **72** with dibenzylidene acetone **140**

At the time, this was the solitary example of this reaction-type, affording the fused [6,5,7] tricycle **141** as a mixture of diastereomers, it is worth noting that this was the solitary example of such a transformation and only symmetrical divinyl ketones (DVKs) were explored.

2. GOLD-CATALYSED DOUBLE FRIEDEL-CRAFTS ALKYLATION OF INDOLE WITH ENYNONES

2.1 Background Information

Work previously undertaken in the Carbery group has sought to exploit divinyl ketones (DVKs) as double-electrophiles for the double Friedel-Crafts alkylation of indole.¹²³



Scheme 46 – Double alkylation of indole **72** by DVK **142**

This Brønsted acid catalysed transformation yields a complex fused-tricyclic indole product **143** in a highly regio- and diastereoselective manner. The importance of this tricyclic scaffold can be highlighted by three structurally related indoles, recently reported in medicinal chemistry literature as offering potent biological activity.

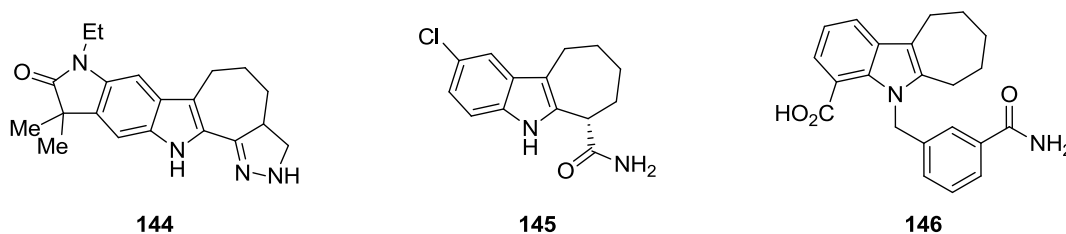


Figure 7 – Three biological active indole containing [6,5,7] tricycles. Indole **144**, carboxamide **145** and Indolo-carboxylic acid **146**.

Indole **144** is a potent aurora kinase inhibitor, displaying quantitative bioavailability in mouse model tumour xenographs.¹²⁴ Carboxamide **145** represents the most potent SIRT1 inhibitor to date, and as such has been suggested as a lead towards therapeutics.¹²⁵ Indolo-carboxylic acid **146** is a potent and selective fatty-acid binding protein (FABP) inhibitor.¹²⁶ It is worth noting that the specified [6,5,7] scaffolds offered

maximum biological activity in their respective assays when compared to the analogous [6,5,6] and [6,5,5] scaffolds.

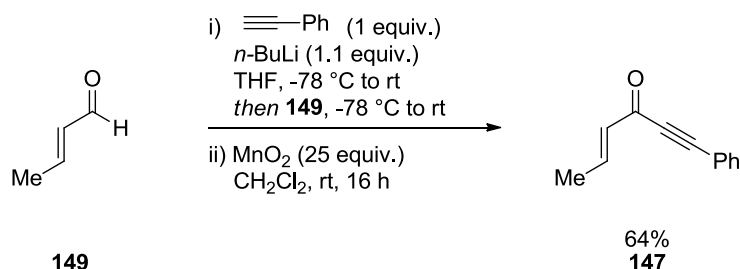
2.2 Concept Development

Building on the Brønsted acid catalysed annulation of indole by DVKs we sought to expand the scope of such transformations. With this in mind we chose to consider structurally related ketonic double electrophiles, such as enynones, with the view to forming novel, functionalised tricyclic indole structures.



Figure 8 – Enynone **147** and potential tricycle **148**

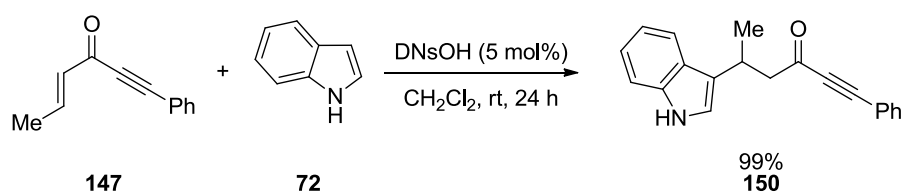
With a clear medicinal rationale, we reasoned that a novel and flexible approach to such [6,5,7]-tricyclic indoles might open new areas of chemical space for exploration in a small-molecule discovery context. Two requirements were identified for the synthesis of the desired [6,5,7]-tricyclic core; the facile synthesis of enynones with the ability to incorporate a range of functionality, and a suitable catalyst to promote the reaction. It was decided to investigate ketone **147** as the initial substrate, as both Michael acceptors have differing steric and electronic considerations. It was concluded that the most facile method for the synthesis of **147** would be *via* the addition of a metal-acetylide to an unsaturated aldehyde, followed by oxidation of the resultant alcohol.



Scheme 47 – Enynone **147** synthesis

Following lithiation of phenylacetylene and addition to crotonaldehyde, an alcohol is produced, however attempts to isolate this intermediate gave poor yields (~20%), whereas oxidation of the crude reaction material gave the desired enynone **147** in improved yield.

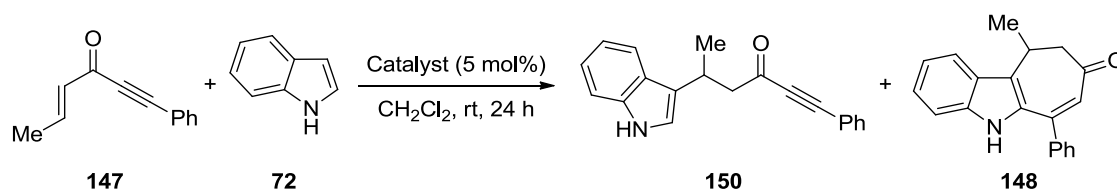
With the requisite enynone in hand, an initial examination was conducted using enynone **147** and indole **72** in the presence of the previously successful strong Brønsted acid promoter, 2,4-dinitrobenzenesulfonic acid.



Scheme 48 – Brønsted acid-catalysed mono-alkylation of indole

The clean intermolecular enone Friedel-Crafts reaction was observed under acidic conditions in quantitative yield, however no cyclised product **148** was observed. The lack of annulation could be due to the inability of the Brønsted acid to sufficiently activate the ynone to nucleophilic attack. To encourage the formation of the desired tricyclic compound, a range of π -acidic metals were examined in the hope of facilitating the annulation.

Table 1 – Catalyst screen for the double alkylation of indole 72 with enyne 147



Entry	Catalyst	147:150:148 ^[a] [%]
1	DNsOH	0:100:0
2	FeCl ₃ ·6H ₂ O	25:75:0
3	PtCl ₂	90:10:0
4	CuOTf	30:70:0
5	PdCl ₂	83:17:0
6	Pd(PPh ₃) ₂ Cl ₂	12:88:0
7	AuPPh ₃ Cl	100:0:0
8	AuPPh ₃ Cl/AgSbF ₆	100:0:0
9	NaAuCl ₄ ·2H ₂ O	33:45:22

[a] Determined by ¹H NMR analysis of crude reaction mixture

Although the majority of the Lewis acidic metals evaluated promoted the Michael addition to the enone, they failed to provide the annulated product **148**. Pt(II) and Pd(II) complexes have both been shown to activate alkynes under a variety of conditions, however were unable to facilitate the cyclisation of this substrate.^{110, 127} Surprisingly, Au(I) also proved to be unsuccessful, failing even to promote the initial Michael addition to the enone. As shown in chapter one, Au(I) has been shown to be highly alkynophilic, allowing for the addition of a range of nucleophiles to alkyne containing substrates. However, due to the quantitative isolation of **147**, we can see the Au(I) catalyst is not sufficiently activating to promote the intermolecular addition of indole to the enone in this context. The sole exception was the readily available sodium tetrachloroaurate(III) dihydrate, offering 22% conversion after 24 hours, however, mono-addition product **150** and starting material **147** were also present. The regiochemistry of the annulated product **148** was determined by NOESY spectroscopy, with NOEs between the 5-position proton of indole and the methyl group and the N-H of indole with the ortho protons of the phenyl ring.

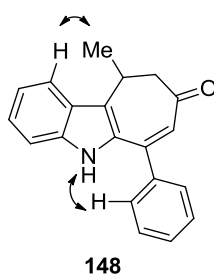
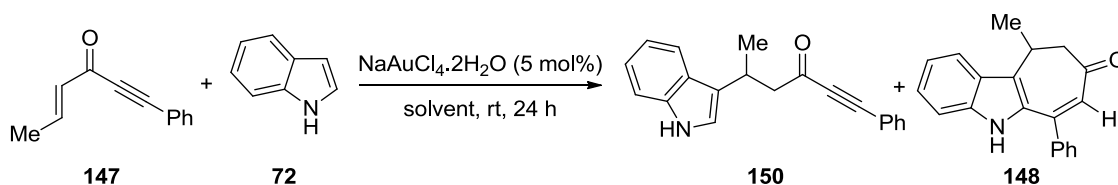


Figure 9 – NOEs that confirm regioisomer of annulated product

With the aim of increasing the conversion of this transformation, solvent optimisation was undertaken.

Table 2 – Solvent screen



Entry	Solvent	147:150:148 ^[a] [%]	Yield [%]
1	CH ₂ Cl ₂	33:45:22	-
2	PhMe	50:49:1	-
3	Et ₂ O	40:30:30	-
4	DMF	35:65:0	-
5	EtOH	0:38:62	-
6	MeCN	0:0:100	96
7	MeCN ^[b]	0:0:100	99
8	MeCN ^{[b], [c]}	0:0:100	98

[a] Determined by ¹H NMR analysis of crude reaction mixture. [b] 2 mol% catalyst used. [c] Reaction conducted for 4 h.

Toluene, a non-polar, aprotic solvent was shown to be a poor reaction solvent, providing only a limited quantity of **148**. Dimethylformamide (DMF) also failed to facilitate the annulation, although this may not be surprising as DMF can bind to Au, potentially limiting its reactivity.¹²⁸ Diethyl ether only shows marginal improvement over dichloromethane. However when highly polar solvents (Entries 5-8) are used a

dramatic increase in tricycle **148** formation occurs. It is clear that in acetonitrile the reaction efficiency is markedly improved (Entries 6-8), with the ability to reach full conversion within four hours with only 2 mol% catalyst loading. Pleasingly, this reaction affords a single regioisomer, with initial addition to the enone occurs at the C-3 position of indole.

To establish that the Michael addition product **150** is in fact a reaction intermediate *en route* to the [6,5,7]-tricycle **148**, *in situ* reaction monitoring by ^1H NMR was conducted.

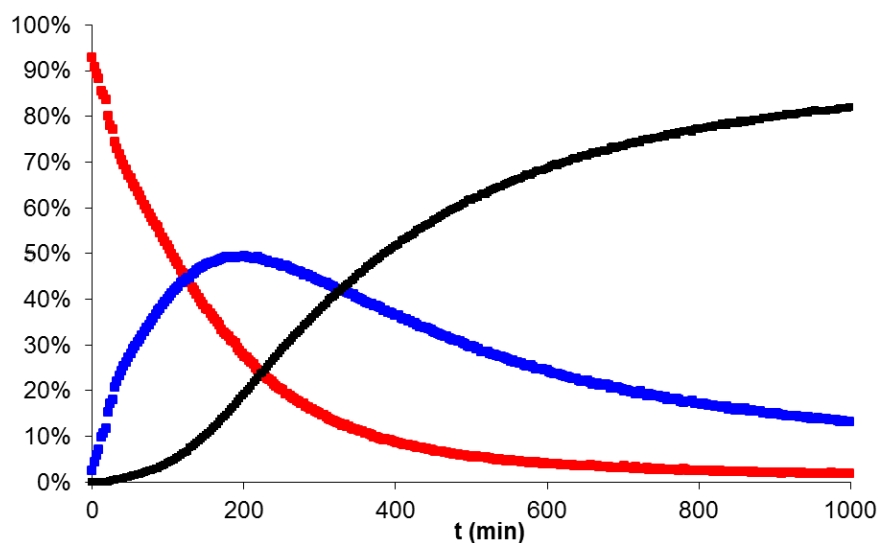


Figure 10 – ^1H NMR monitoring of tandem cascade reaction (CD_3CN at 20°C ; 500 MHz) ■=147, ■=150, ■=148

As can be seen in figure 10, mono-addition product **150** is present (20%) before the observable formation of tricycle **148**, with associated consumption of **147**. There are two possible mechanisms that are possible for the annulation of **150**; the direct C-2 addition of indole to the ynone fragment to provide **148**, or C-3 addition of indole to the ynone affording spirocycle **151**, followed by migration of the α,β -unsaturated moiety to afford **148**.

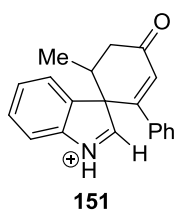
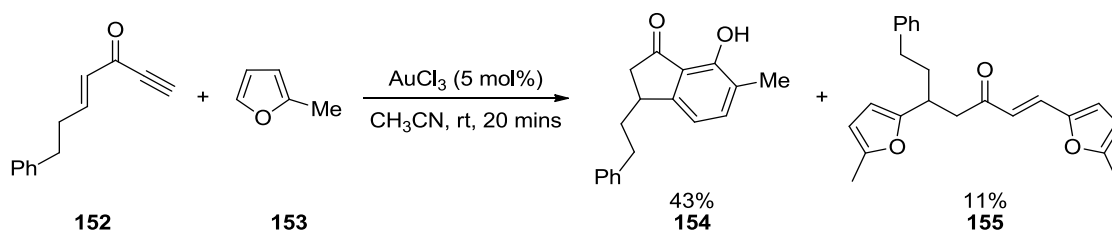


Figure 11 – Possible spirocyclic intermediate

During the ^1H NMR monitoring experiment it is worth noting that no signal indicative of the spirocyclic compound were observed, discounting this as the mechanism for the formation of **148**.

The ability for enynones to act as double-electrophiles in this reaction is in stark contrast to the reaction of enynones with furan **152** reported by Hashmi and Grundl.¹²⁹



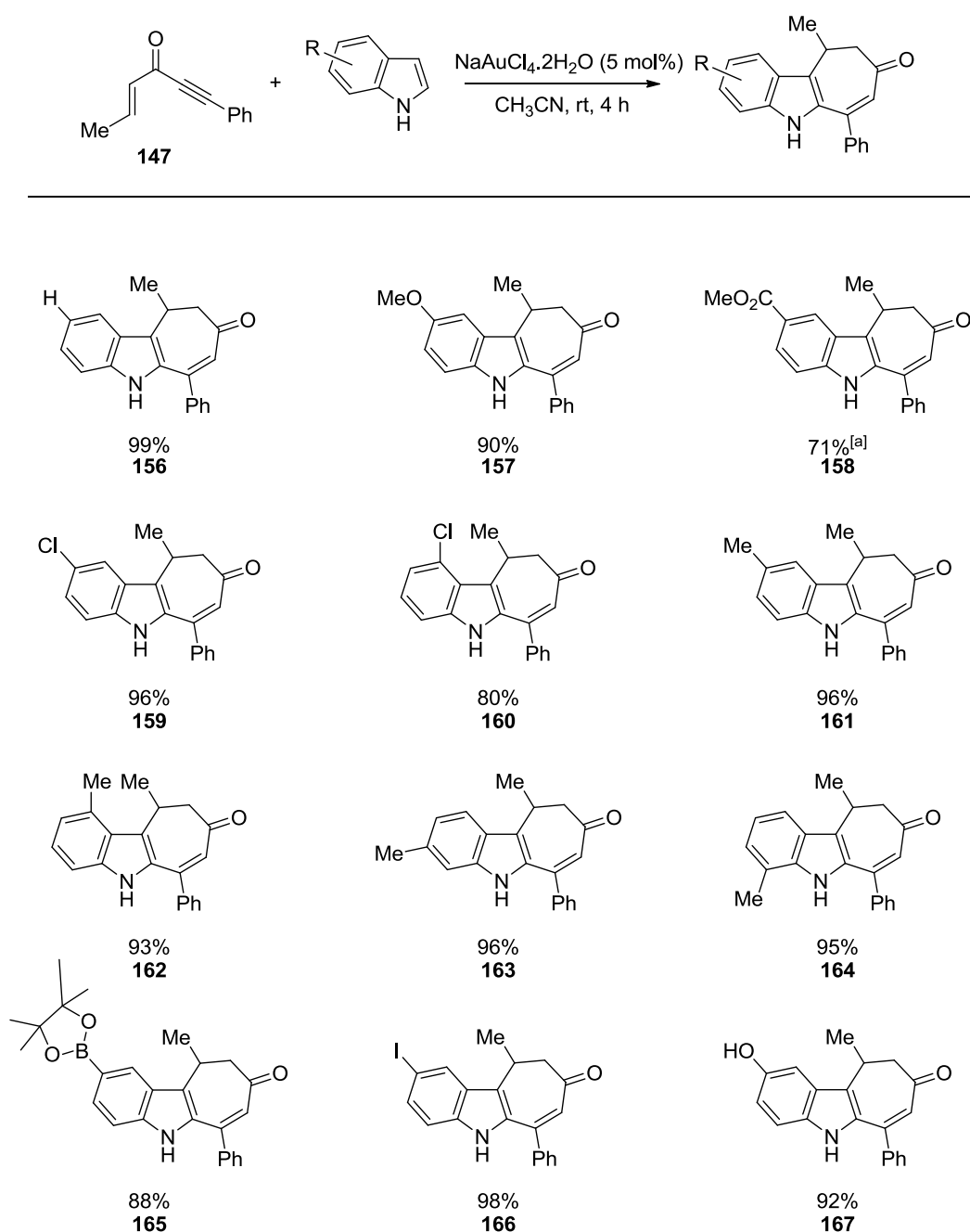
Scheme 49 – Addition of 2-methylfuran **153** to enynone **152**

After initial Michael addition to the enone, the resultant intermediate undergoes cycloisomerisation rather than a second alkylation of furan. However, a handful of examples did furnish the addition of two furan molecules into enynone **152** as the minor product.

2.3 Indole Scope

With optimised conditions in hand, a range of indoles were examined with a view to demonstrating the flexibility and diversity of this reaction protocol.

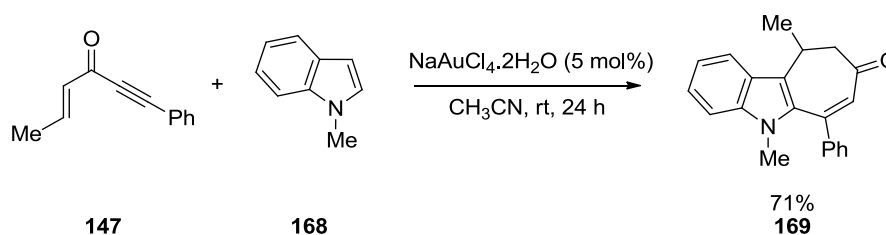
Table 3 – Indole scope



[a] Reaction conducted for 24 h.

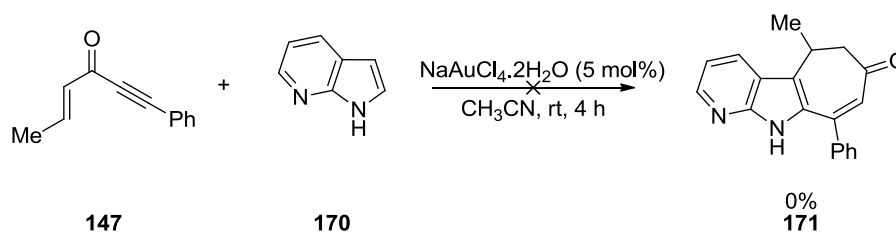
As can be seen, electron-rich indoles are compatible with this methodology, furnishing the relevant [6,5,7]-tricycle **157** in excellent yield. Electron-deficient indoles are also tolerated, however in the case of methyl indole-5-carboxylate an extended reaction time is required to allow for full conversion of starting material. The indole annulation is also unperturbed by substitution on the benzenoid fragment of indole, judged by the range of methylindole and chloroindole regioisomers able to participate in the reaction, affording tricycles **159-164**. The functional group tolerance of this reaction is demonstrated by the ability to utilise an unprotected hydroxyl group in this tandem process, **167**. In particular, the incorporation of synthetic handles, such as boronate ester **165** and iodide **166**, offers the opportunity for further synthetic elaboration post-reaction. The commercial availability of the starting materials and ease of synthesis of a diverse array of indole derivatives, coupled with the reactions functional group tolerance, gives this transformation wide applicability.

Previous studies into the Brønsted acid-catalysed annulation of indoles carried out in our group showed that *N*-substitution of indole is not compatible with the reaction.¹³⁰ In the gold-catalysed reaction, *N*-methyl indole **168** reacts smoothly to give the desired product **169**, however, the Au(III) catalyst has to be added portionwise in order to achieve full conversion to product.



Scheme 50 – Double alkylation of *N*-methylindole **168** by enynone **147**

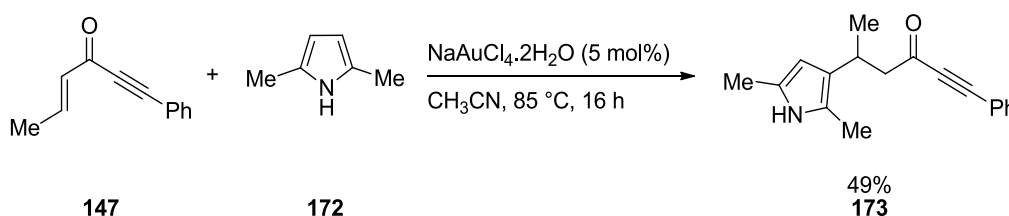
Another important class of heterocycles are azaindoles; formally 1H-pyrrolo[2,3-*x*]pyridines – where *x* describes the position of the pyridyl nitrogen. Azaindoles are a class of indole derivatives with equally diverse biological applications.¹³¹



Scheme 51 – Failed alkylation of 7-azaindole

The attempted double alkylation of 7-azaindole **170** returned a quantitative amount of starting material, with even highly forcing conditions previously used for the Michael addition of azaindoles (EtOH, 140 °C, sealed tube) failing to provide even the mono-addition product.¹³² Interestingly, the reaction was not fully homogeneous, containing visible particulates, and it has been shown previously that azaindoles are capable of binding to a number of metals, including silver and platinum.¹³³ The lack of reactivity in our case may demonstrate the poisoning of the catalyst by the pyridyl nitrogen of the azaindole. 4-, 5-, and 6-azaindoles were also subjected to the reaction conditions, however, as with 7-azaindole no reaction occurred.

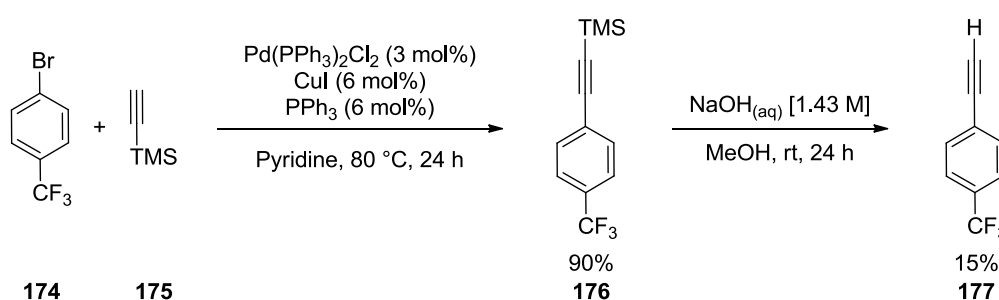
To explore the use of alternative nucleophiles, 2,5-dimethyl pyrrole **172** was employed as the double nucleophile, with the aim of synthesising structurally related products.

Scheme 52 – Mono-alkylation of 2,5-dimethylpyrrole **172** by enone **147**

Unlike indole, pyrrole is most nucleophilic at the C-2 position, however we chose the substrate **172** in which both of these positions have been substituted. This decision was in attempt to avoid the potential of one pyrrole unit adding to two enynone units, with the reduced nucleophilicity of the C-3 position helping to temper the reactivity. Although the reaction was heated to reflux for 16 hours, only the initial Michael-addition product **173** was formed, with the return of the remaining starting material **147**.

2.4 Enynone Scope

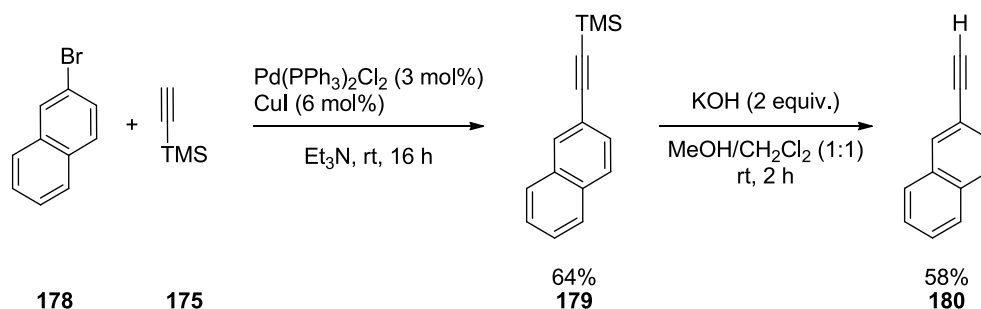
Having assessed the generality of this reaction with regards to the indole reaction partner, a series of experiments were undertaken to synthesise a range of enynones bearing a variety of functional groups in an attempt to probe the limitations of this tandem process. Although there are a large number of commercially available functionalised terminal alkynes, to fully explore the structural scope of the Au(III)-catalysed double alkylation of indole, a number of non-commercially available acetylenes were first synthesised.



Scheme 53 – Synthesis of 1-ethynyl-4-(trifluoromethyl)benzene **177**

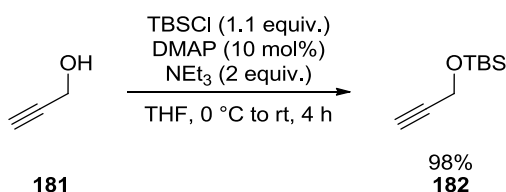
Following the procedure layed out by Jenny *et al.*, Sonogashira coupling of ethynyltrimethylsilane **175** and aryl bromide **174** proceeded smoothly.¹³⁴ Deprotection of **176** was then necessary, with removal of the silyl group occurring quantitatively, as determined by ^1H NMR conversion. Purification of the terminal acetylene **177** proved difficult due to co-elution with by-products during flash chromatography, however it was possible to isolate **177** in poor yield *via* distillation under reduced pressure.¹³⁵

Another alkyne to be synthesised was 2-ethynylnaphthalene **180** in order to ascertain if additional alkyne substitution would be tolerated in the double addition. Using the procedure reported by Pu *et al.*, Sonogashira coupling and subsequent deprotection afforded terminal acetylene **180** in good yield.¹³⁶



Scheme 54 – Synthesis of 2-ethynynaphthalene 180

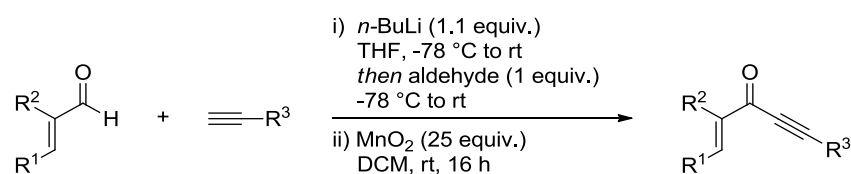
To incorporate additional heteroatom functionality into the tricyclic product, it was envisaged that a propargyl alcohol could be utilised in the acetylide addition to crotonaldehyde. In order to avoid deprotonation of the alcohol in the following step, prop-2-yn-1-ol **181** was protected with *tert*-butylchlorodimethylsilane (TBSCl) to afford the silyl ether **182** in near quantitative yield.¹³⁷



Scheme 55 – Silyl protection of prop-2-yn-1-ol 181

With the requisite terminal alkynes in hand, and due to the modularity of the synthesis of enynones, a range of aliphatic and aromatic groups were able to be incorporated into the enynone at various positions.

Table 4 – Enynone synthesis



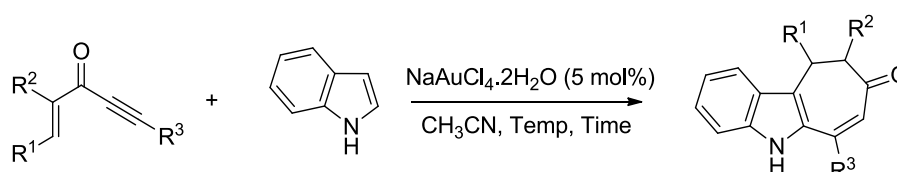
Entry	R ¹	R ²	R ³	Product	Yield [%]
1	Me	H	4-MeC ₆ H ₄	183	60
2	Me	H	4-OMeC ₆ H ₄	184	52
3	Me	H	4-CF ₃ C ₆ H ₄	185	16
4	Me	H	2-Naphth	186	56
5	Me	H	<i>n</i> Bu	187	48
6	Me	H	CH ₂ OTBS	188	67
7	Me	H	TMS	189	51
8	Me	Me	Ph	190	57
9	<i>i</i> Pr	H	Ph	191	58
10	Ph	H	Ph	192	58
11	Ph	H	2-Naphth	193	54
12	Ph	H	<i>n</i> Bu	194	42
13	H	H	<i>n</i> Bu	195	44
14	H	H	Ph	196	48
15	H	Me	Ph	197	55

To determine the electronic requirements of the reaction, an electron-rich and electron-poor substrate, **184** and **185** respectively, were synthesised. The poor yield for the synthesis of **185** may be a result of the electron-withdrawing ability of the trifluoromethyl group. To examine the electronic and steric restrictions on the reaction **186-197** were synthesised. The synthesis of enynones containing additional heteroatom functionality was conducted by the synthesis of protected alcohol **188** (Table 4, entry 6). Addition of aromatic functionality (entries 10-12) will alter the sterics and electronics of the α,β -unsaturated system, providing additional conjugation, as well as the ability to potentially stabilise charged intermediates. In particular, enynone **194** has an alkyl-group appended to the alkyne, allowing the electronics of both electrophilic centres to

be altered. Entries 13-15 bear no substitution on the alkene terminus of the enone, again altering the steric and electronics of the system. Enynone **190** was synthesised in order to evaluate the potential diastereoselectivity of the initial Michael addition (entry 8).

With a range of structurally diverse enynones synthesised, the scope of the Au(III)-catalysed cascade was evaluated.

Table 5 – Enynone scope



Entry	Substrate	R ¹	R ²	R ³	Time [h]	Temp [°C]	Product	Yield [%]
1	183	Me	H	4-MeC ₆ H ₄	6	23	198	98
2	184	Me	H	4-OMeC ₆ H ₄	24	23	199	82
3	185	Me	H	4-CF ₃ C ₆ H ₄	16	23	200	73
4	186	Me	H	2-Naphth	8	23	201	81
6	187	Me	H	<i>n</i> Bu	24	82	202	79
7	188	Me	H	CH ₂ OTBS	18	23	203	0 ^[a]
8	189	Me	H	TMS	18	82	204	98 ^[b]
9	191	<i>i</i> Pr	H	Ph	18	23	205	72
10	190	Me	Me	Ph	18	23	206	73 ^[c]

[a] Based on ¹H NMR analysis of crude reaction mixture. [b] yield of mono addition product. [c] 4:1 dr based on ¹H NMR analysis of crude reaction material

As can be seen the reaction can tolerate electron-rich and poor aromatic ynones substitution (Table 5, entry 1-3). Increased steric bulk of the enynone is also permitted in this reaction, with naphthyl enynone **186** and *iso*-propyl enynone **191** reacting well (entries 4 and 9). The reaction of **188** provided no product by ¹H NMR analysis of the crude reaction mixture, even when the reaction mixture was heated to reflux (entry 7). TMS enynone **189** provided quantitative return of the Michael addition product, with no

annulated product being isolated (entry 8). When an alkyl ynone fragment is utilised, the reaction rate is markedly slower than enynones bearing aromatic functionality on the ynone, with heating to reflux necessary to promote the annulation step (entry 6). Enynone **190** gave a 4:1 *syn/anti* ratio of tricyclic product **206** based on ^1H NMR analysis of the crude reaction material. This diastereoselectivity was confirmed by single crystal X-ray diffraction analysis of the major isomer.

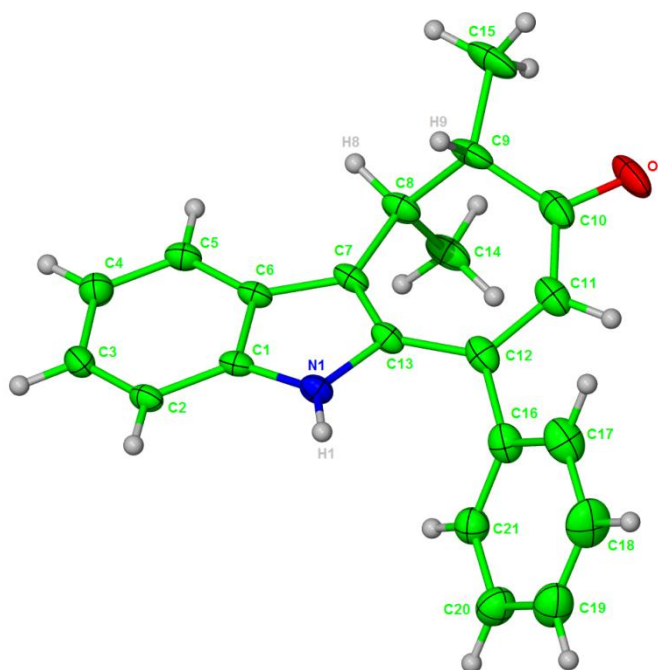
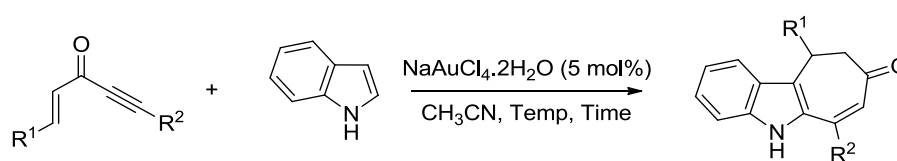


Figure 12 – XRD analysis of of tricycle 206

Table 6 – Aromatic enone scope

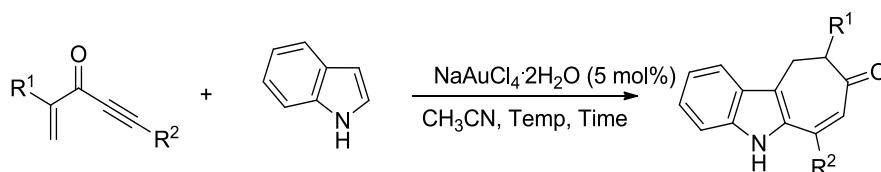


Entry	Substrate	R1	R2	Time [h]	Temp [°C]	Product	Yield
1	192	Ph	Ph	24	82	207	77
2	193	Ph	2-Naphth	24	23	208	97
3	194	Ph	<i>n</i> -Bu	72	82	209	47

When compared to the alkyl enones (Table 5), aryl enones required more forcing conditions to promote reaction. Extended reaction time was required for the reaction of

194, containing both an aromatic enone and alkyl ynone fragment (Table 6, entry 3), with both starting material and mono-addition products also being isolated. Observation of the reaction by TLC shows that mono-addition occurs quickly, although not as rapidly as with alkyl enones, and annulation is slow. The alkyl ynone fragment is more electron-rich than its aromatic analogues, with the increased electron-density on the alkyne potentially lowering the electrophilicity of the ynone, thus retarding the reaction rate.

Table 7- Terminal enone scope

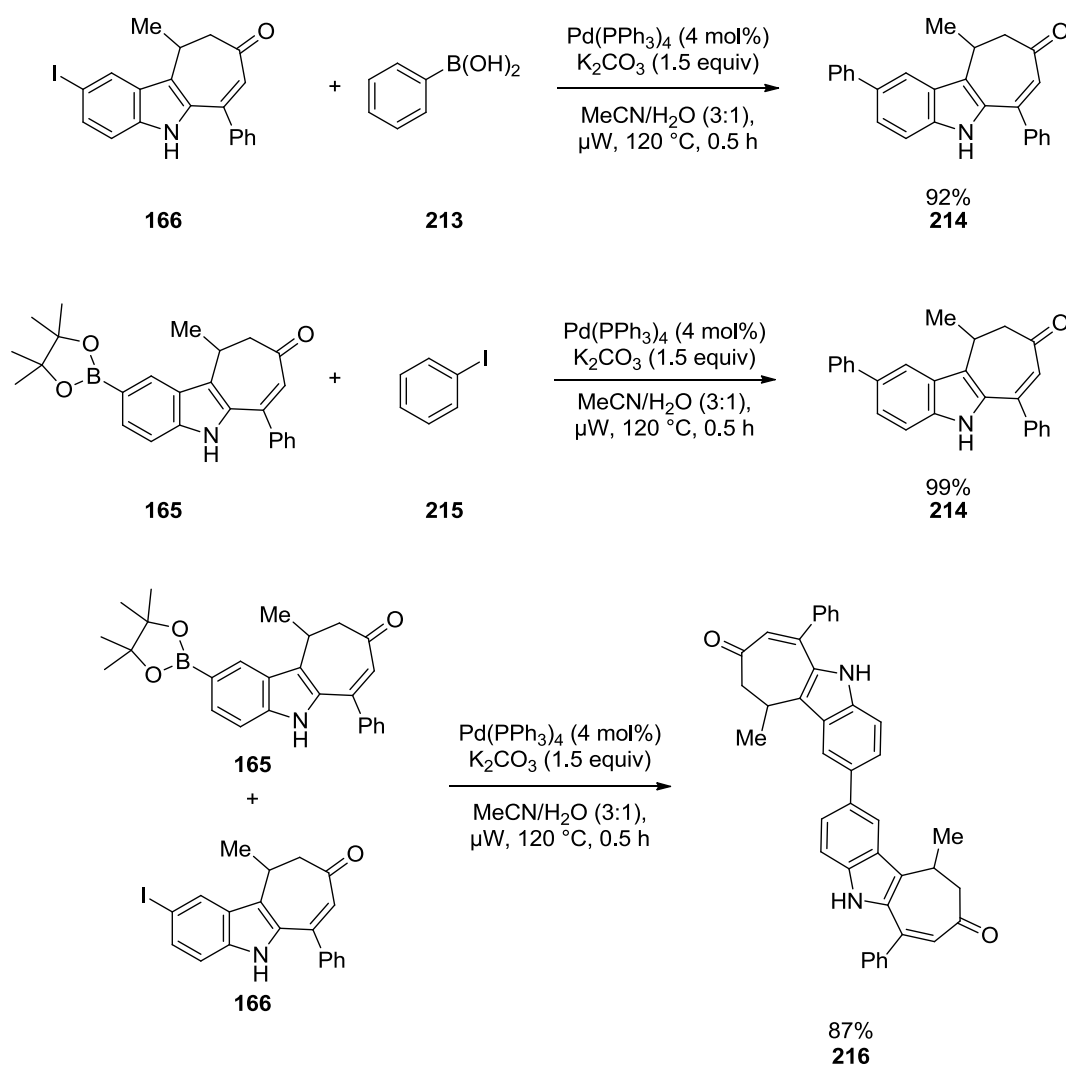


Entry	Substrate	R1	R2	Time [h]	Temp [°C]	Product	Yield [%]
1	195	H	Ph	12	23	210	99
2	196	H	nBu	96	82	211	60
3	197	Me	Ph	8	23	212	76

Terminal enones are also tolerated in this reaction, with the reaction of α -substituted enone **197** proceeding well (Table 7, entry 3), albeit in lower yield than the fully unsubstituted enone **195** (entry 1). Mirroring the trend seen previously, alkyl ynone **196** requires forcing conditions to facilitate annulation.

2.5 Product elaboration

To display the synthetic utility of our iodo- and boronic ester- functionalised tricycles **166** and **165**, it was decided to carry out simple Suzuki cross-couplings with phenylboronic acid **213** and iodobenzene **215** respectively.¹³⁸



Scheme 56 – Suzuki coupling reaction of **165** and **166**

Both tricycles are excellent coupling partners, with the cross-coupling reactions proceeding in near quantitative yield. This is further demonstrated by the coupling of **165** and **166** with each other, affording formal dimer **216**.

2.6 Mechanistic Insights

Having developed the gold-catalysed double alkylation of indole with enynones, it was decided to probe the mechanism of this transformation, and elucidate the role of the gold(III) catalyst. Arcadi *et al.* hypothesised the presence of a C-3 aured indole intermediate **217** in the conjugate addition to α,β -unsaturated ketones.¹²²

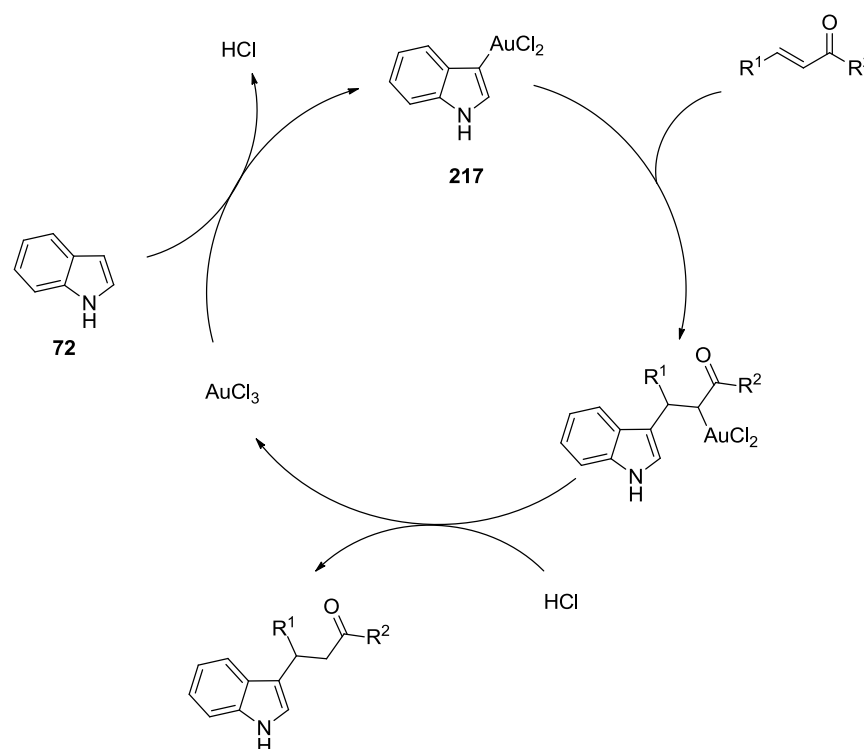
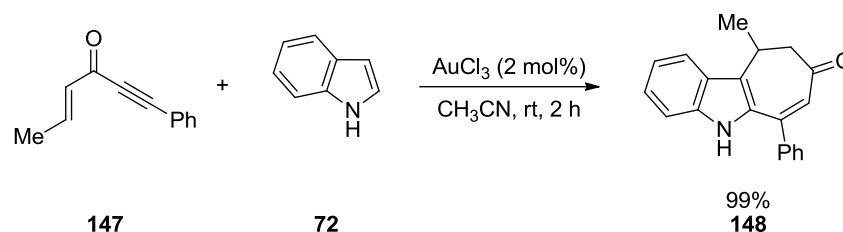


Figure 13 – Arcadi's proposed mechanism for Au-catalysed Michael addition of indole

Regioselective nucleophilic attack of indole onto Au(III) chloride gives an indolyl-gold(III) species **217**, which subsequently undergoes 1,4-addition to the α,β -unsaturated ketone to give a σ -alkyl-gold species. The organogold intermediate undergoes protodeauration, facilitated by the proton liberated in the electrophilic aromatic substitution step. This hypothesised mechanism is supported by mass spectroscopy. When stoichiometric amounts of sodium tetrachloroaurate (III) dihydrate and indole are combined the positive ion electrospray mass spectra (ESI-MS) shows ion peaks at $m/z = 348$ and 350 , which match calculated isotope distribution patterns for $[\text{indolyl-AuCl}]^+$. When C-3 substituted indoles were utilised in the reaction, C-2 alkylated products were isolated, however it was not explicitly stated that C-2 auration was in fact occurring.

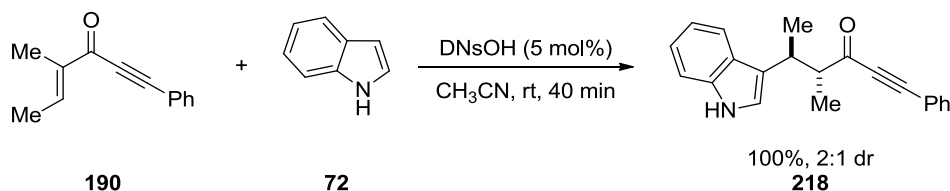
A number of gold-catalysed transformations found in the literature utilise sodium tetrachloroaurate(III) to facilitate reaction, however it has been assumed that gold(III) chloride is the catalytically active species, generated *in situ* from the sodium tetrachloroaurate pre-catalyst.¹²² To ascertain whether gold(III) chloride is the catalytically active species within our reaction, gold(III) chloride was employed in the double alkylation of indole **72** with **147**.



Scheme 57 – Test reaction using gold(III) chloride as catalyst

The reaction proceeds smoothly, affording **148** in quantitative yield after only two hours, a notable increase over the rate witnessed when sodium tetrachloroaurate is employed (4 hours). The observed increase in rate for this reaction may be attributed to the gold catalyst already being in its active state. This result, combined with literature precedence,¹²² allows us to be confident that gold(III) chloride is the catalytically active species in our reaction.

To confirm the mechanism proposed by Arcadi *et al.* for the intermolecular conjugate addition of indole to enones, a number of experiments were designed. First to ascertain if the gold(III) catalyst is acting as a traditional oxophilic Lewis acid, dimethyl enynone **190** was subjected to acid catalysed conditions.

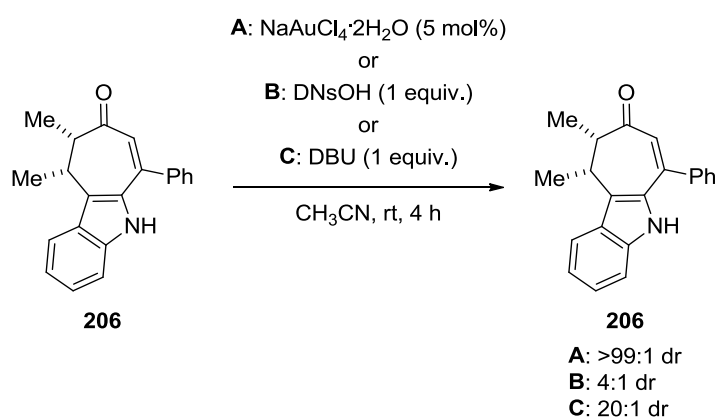


Scheme 58 – Acid catalysed mono-alkylation using dimethyl enynone **190**

The mono-addition product **218** formed in this reaction had a diastereomeric ratio of 2:1 in favour of the *anti*-product (see appendix 6.3.4), whilst this is the same relative

stereochemistry as in the annulated product, the diastereomeric ratio is marginally different from the gold-catalysed transformation (4:1 *syn/anti*). Under acid catalysed conditions, ketone **218** is readily enolised, with subsequent tautomerisation affording a thermodynamic mixture of diastereomers. This would indicate that the gold catalysed transformation may be under kinetic control, due to the discrepancy between diastereomeric ratios.

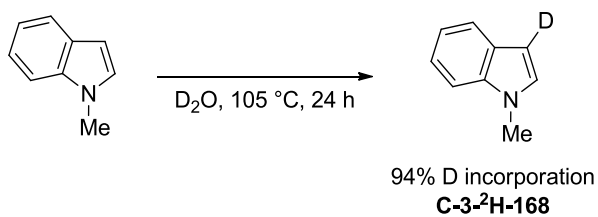
To confirm this hypothesis the major diastereomer of **206** was resubjected to the gold-catalysed reaction conditions, as well as being subjected to acidic and basic conditions.



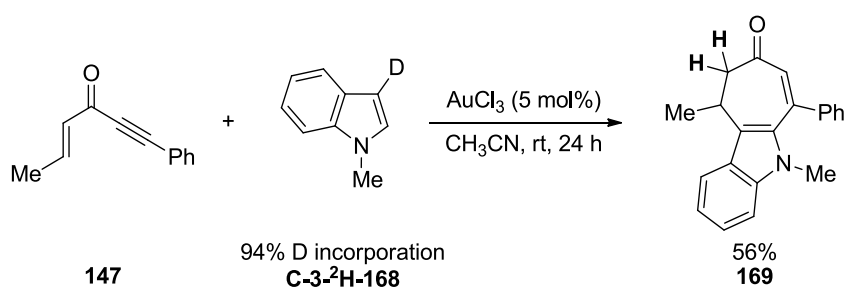
Scheme 59 – Subjection of **206** to gold-catalysed conditions, acidic and basic conditions

Resubjection of **206** to the gold(III)-catalysed reaction conditions resulted in no loss of diastereoselectivity, however both acidic and basic conditions showed degradation of diastereomeric excess. These findings help support the hypothesis that gold is not acting as an oxophilic Lewis acid in our transformation, as no loss of diastereoselectivity is witnessed under gold-catalysed conditions.

As a final test to confirm our belief of C-3 auration, it was necessary to synthesise **C-3-²H-168**. As the C-3 position of indole is the most nucleophilic, simply stirring in deuterium oxide was sufficient to provide deuterium enriched *N*-methyl indole.¹³⁹

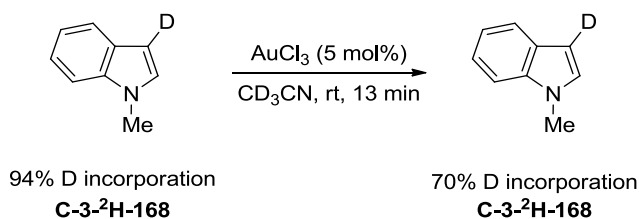
Scheme 60 – Formation of C-3-²H-168

Investigation then began to assess if the deuterium content of **C-3-²H-168** would be transferred to the annulated product under the Au(III) catalysed reaction conditions.

Scheme 61 – Reaction of C-3-²H-168 with enynone 147

Interestingly no deuterium was incorporated into the product **169**, contrary to what might be expected for a Michael addition. It was believed that the Au(III) catalyst was solely responsible for the loss of deuterium incorporation, as the deuterium content of **C-3-²H-168** is retained for over four days in acetonitrile alone.

To support this hypothesis, a ¹H NMR experiment was devised in which **C-3-²H-168** would be subjected to gold catalysed conditions, mirroring those in Scheme 62.

Scheme 62 – Subjection of C-3-²H-168 to Au-catalysed reaction conditions

It was found that the NMR solvent contained a small amount of water, ~ 11% relative to indole. When gold(III) chloride was added there was a significant reduction of

deuterium content of indole **C-3-²H-168** almost immediately, as well as an associated consumption of all water in the NMR solvent. This would indicate that the gold(III) chloride has replaced the deuterium at C-3 with both protons from each water molecule present in the sample. The speed of this deuterium displacement indicates the interaction of gold(III) and the C-3 position of indole, again implying that auration of indole as the mechanism for the intermolecular alkylation of indole.

The rapid auration of indole **72** at the 3-position, along with the retention of diastereoselectivity upon subjection of tricycle **206** to gold-catalysed conditions, help to support the mechanism proposed by Arcadi *et al.* (Figure 12) for the intermolecular alkylation of indole.¹²²

Although the role of the gold catalyst in the intermolecular alkylation of indole is now understood, the mechanism of action of Au(III) in the intramolecular annulation is still not clear. With the aim of clarifying the mechanism of our optimised double alkylation of indole, a ¹H NMR experiment was devised. It was decided to subject mono-addition product **219** to the reaction conditions, in order to potentially observe the *in situ* formation of any C-2 aured intermediates, such as **220**. Stoichiometric quantities of sodium tetrachloroaurate(III) would be necessary to allow for quantitative analysis of any relative reduction of C-2 protonation, with butyl ynone **219** chosen due to its slow reaction times.

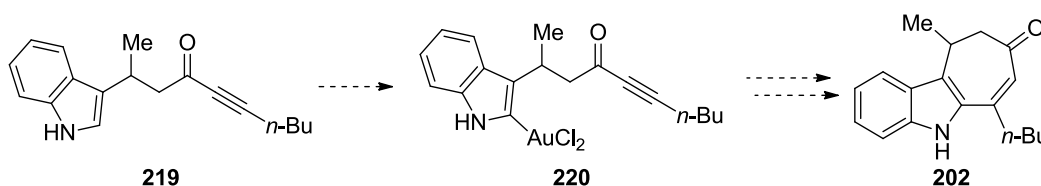
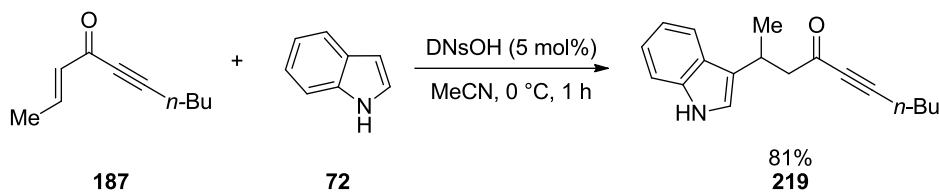
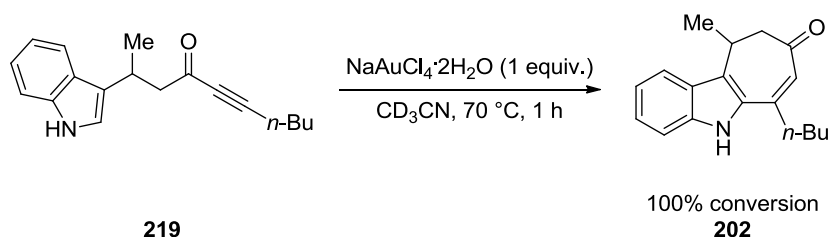


Figure 14 – Possible intermediate **220** formed as part of the double alkylation of indole

Making use of the Brønsted acid-catalysed Michael reaction, the test substrate **219** was synthesised for the ¹H NMR experiment.

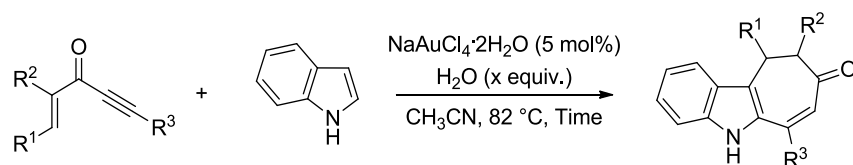
Scheme 63 – ^1H NMR substrate synthesis

With the required substrate in hand: **219** in CD_3CN was added to a dry NMR tube followed by addition of sodium tetrachloroaurate(III) dihydrate. Unfortunately, resolution of the C-2 proton and one of either the C-5/C-6 protons was not possible in acetonitrile, making it unfeasible to assess any degradation of C-2 protonation. However, the reaction was allowed to proceed at 70 °C, giving full conversion after just one hour, a significant rate enhancement over the previous cyclisation of this substrate (24 h, 82 °C, 79% yield), even taking into account the increased catalyst loading.

Scheme 64 – ^1H NMR experiment to assess reaction mechanism

The Au(III) catalyst used in this reaction exists as the dihydrate, and it was reasoned that the presence of two equivalents of water could be responsible for the dramatic rate enhancement seen in the ^1H NMR experiment. To confirm this hypothesis, the previously slow reaction substrates (Table 6, entry 6 and Table 7, entries 1 & 3) were resubjected to the same reaction conditions, however, now with two equivalents of water as an additive.

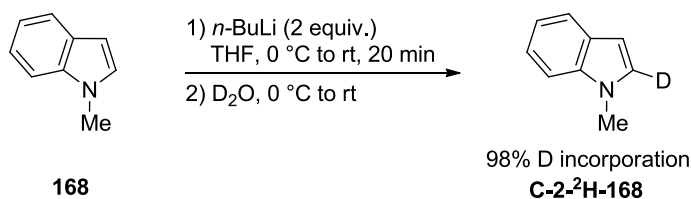
Table 8 – Results of addition of water in the double alkylation of indole by enynones



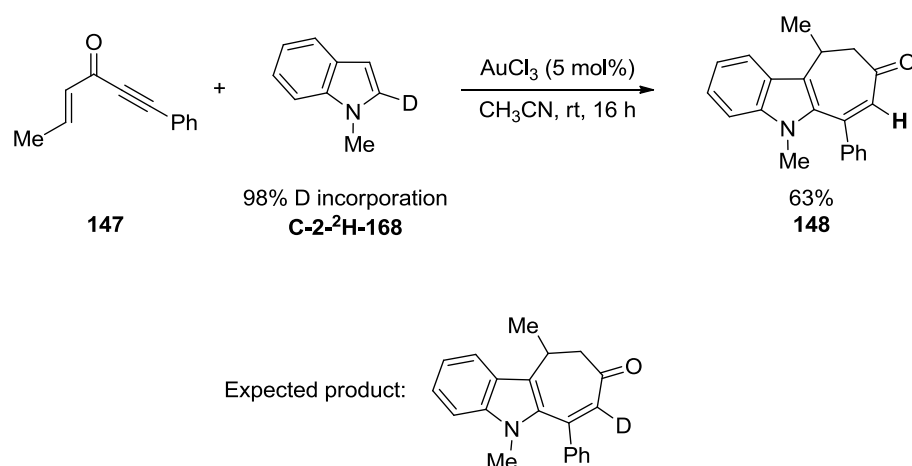
Entry	Substrate	R1	R2	R3	H ₂ O (equiv.)	Time [h]	Product	Yield [%]
1	187	Me	H	<i>n</i> -Bu	0	24	202	79
2	187	Me	H	<i>n</i> -Bu	2	4	202	82
3	192	Ph	H	Ph	0	24	207	77
4	192	Ph	H	Ph	2	3	207	99
5	194	Ph	H	<i>n</i> -Bu	0	72	209	47
6	194	Ph	H	<i>n</i> -Bu	2	18	209	69

As can be seen, the addition of two equivalents of water dramatically reduces the reaction times of the slowest reactions, in some cases the reaction proceeds ~8 times faster than in the absence of water (Table 8, entries 3 & 4). Although this is a very interesting result, it does not help to elaborate the mechanism of action of the gold catalyst.

In an attempt to determine whether Au(III) is capable of aurating the C-2 position of indole, a deuterated indole analogue **C-2-²H-168** was synthesised.¹³⁹

Scheme 65 – Synthesis of 2-deutero *N*-methyl indole, **C-2-²H-168**

Following lithiation at C-2, the reaction was quenched with deuterium oxide to afford **C-2-²H-168** with 98% deuterium incorporation. *N*-Methyl indole was used to circumvent the appearance of protons from any other source in the following reactions.

Scheme 66 – Deuterium studies using C-2-²H-168

The reaction proceeds in a comparable time and yield to that using *N*-methyl indole (Scheme 50), however the deuterated product was not observed, with quantitative proton incorporation in the product. It was hypothesised that proton incorporation could arise from either the use of non-deuterated solvent, or trace amounts of water in the reaction. To investigate these variables a range of experiments were carried out.

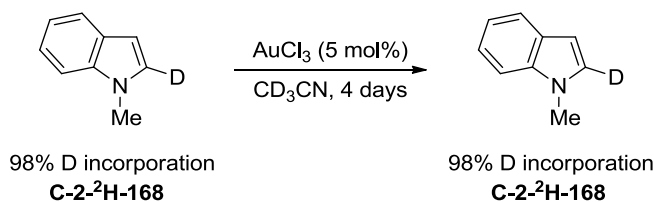
Table 9 – Deuterium incorporation evaluation

147 98% D incorporation C-2-²H-168 148				
Entry	Solvent	Time [h]	Yield [%]	D-incorporation [%]
1	CD ₃ CN	24	44	0
2	CH ₃ CN ^[a]	72	36	0
3	CD ₃ CN ^[a]	72	26	0
4	CH ₃ CN ^[b]	72	30	0
5	CD ₃ CN ^[b]	72	28	0
6	CD ₃ CN ^[c]	72	34	0

[a] 4 Å MS added [b] silylated reaction vessel used [c] Teflon® reaction vessel used

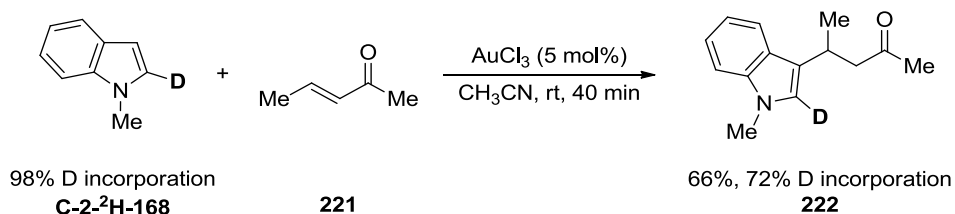
When the reaction was carried out in deuterated reaction media (Table 9, entry 1), no deuterium incorporation was observed in the cyclic product, eliminating the possibility of protonation due to solvent. The other possibility was protonation from trace water in the reaction, however the inclusion of molecular sieves (entries 2-3) did not stop protonation of the product, however reaction times were greatly increased, along with a decrease in yield. To eliminate the possibility of protonation from trace protons associated with the reaction vessel, silylated (entries 4-5) and Telfon® (entry 6) reaction vessels were used, however no deuterium incorporation was witnessed. These findings are highly surprising, with no obvious source of protons being responsible for the lack of deuterium incorporation in **148**. Another interesting finding is the drastic increase in reaction time and lowering of yield when water is fully excluded from the reaction, which may indicate that even adventitious water in the nitrogen supply is playing an important role in the catalytic cycle.

To try and determine at what point in the reaction protonation of **C-2-²H-168** was occurring, it was subjected to the reaction conditions in a ¹H NMR experiment.



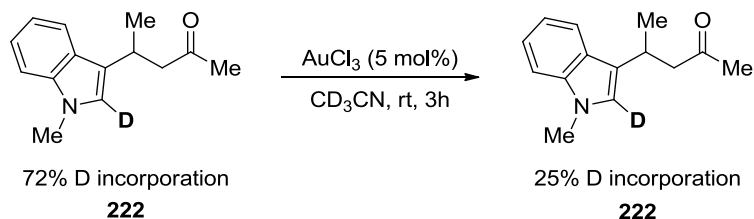
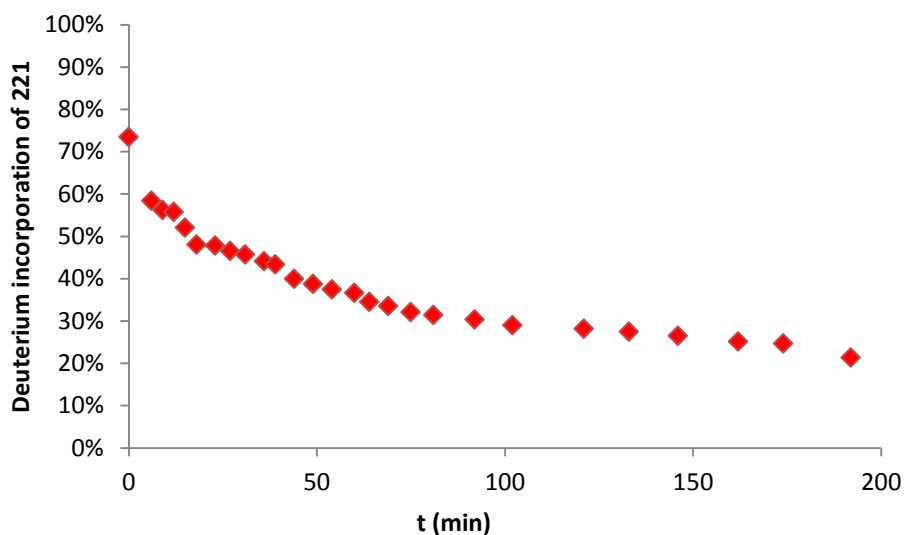
Scheme 67 – Subjection of **C-2-²H-168** to reaction conditions

In stark contrast to the **C-3-²H-168**, no decrease in deuterium content of **C-2-²H-168** was observed even after four days. It was reasoned that when the C-3 position of **C-2-²H-168** is unsubstituted, the gold associates with it rather than the less nucleophilic C-2 position. To test this hypothesis a model substrate was synthesised with similar functionality to the actual reaction substrate for use in ¹H NMR experiments.

Scheme 68 – Synthesis of test substrate **222** for ^1H NMR experiment

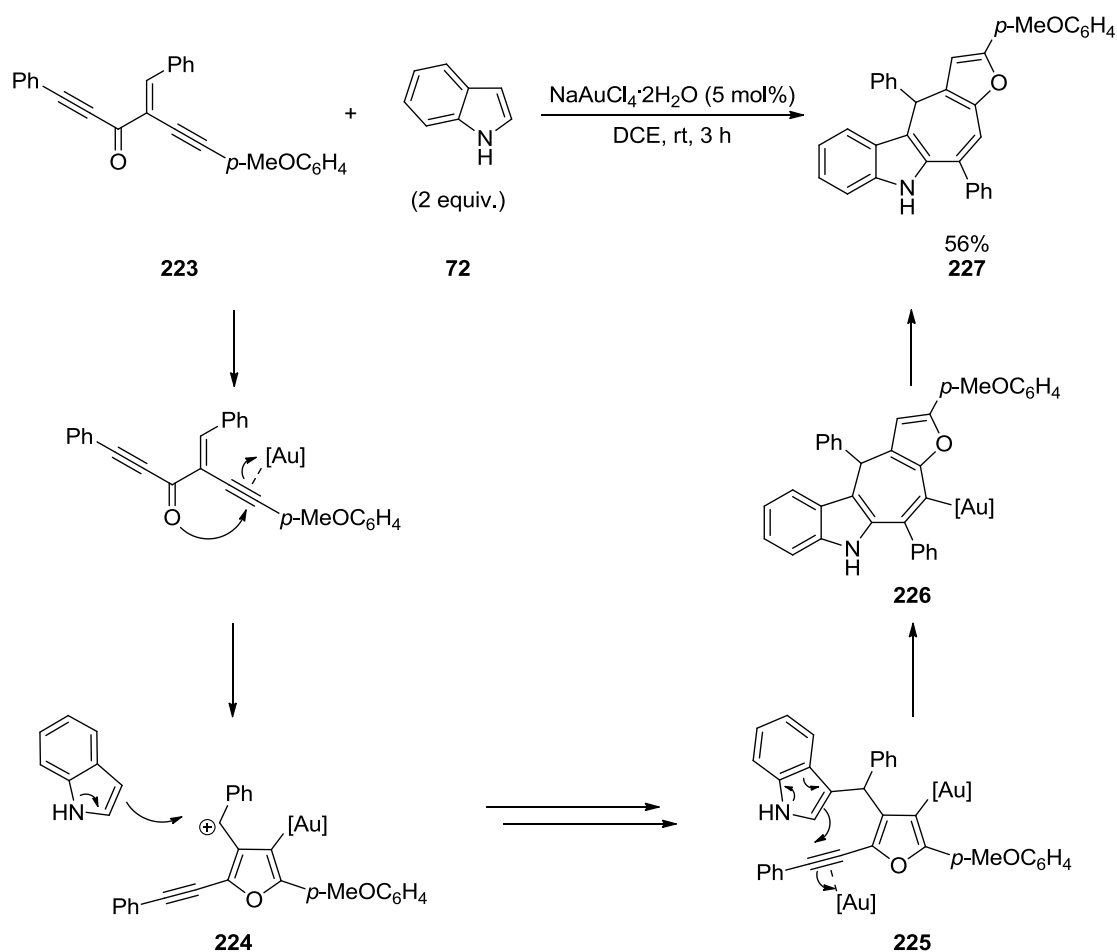
Even after brief subsection to the reaction conditions, a significant decrease in deuterium incorporation is witnessed. This observation, coupled with the previous ^1H NMR experimental results, would indicate that protonation only occurs once the C-3 position of **C-2-²H-168** is substituted.

To quantitatively assess the rate of deuterium-exchange of **222**, the model substrate was resubjected to the reaction conditions and monitored by ^1H NMR.

Scheme 69 – Results of ^1H NMR reactionFigure 15 - ^1H NMR monitoring of test substrate **222** under reaction conditions (CD_3CN at 20°C ; 400 MHz) ■ = deuterium incorporation of **222**

Upon subjection to the reaction conditions, the deuterium content of **222** is rapidly diminished with the rate of protonation slowing over time, however constant degradation of the deuterium content does continue. As was previously demonstrated by the formation of the test substrate, the ^1H NMR experiment reveals that deuterium incorporation at C-2 is diminished under the reaction conditions. The time-scale for this reduction of deuterium content is considerably faster than the reaction timescale, therefore it is possible that protonation occurs before annulation. The replacement of deuterium in this test substrate is however slower than that of the **C-3- ^2H -168**. These findings do indicate the possibility of auration at C-2 after the intermolecular alkylation of indole, however it is not possible to ascertain whether this is the reactive intermediate in the annulation reaction step. It is possible that C-2 auration takes place, but due to the sluggish rate of reaction for the annulation step, it is equally feasible that gold(III) coordination to the ynone is the preferred reaction pathway.

During the course of our research, Liu *et al.* reported the tandem annulation reaction of 1,2-bis(alkynyl)-2-en-1-ones with indole.¹⁴⁰



Scheme 70 – Proposed mechanism for Liu's tandem annulation of 1,2-bis(alkynyl)-2-en-1-ones with indole

As can be seen, this reaction proceeds *via 5-endo-dig* cyclisation of the carbonyl to afford the cationic intermediate **224**, which is subsequently trapped by indole. The proposed mechanism for the indole/ynone cyclisation again supports an alkyne activation pathway.

Based on our findings, a tentative mechanism for the overall reaction is proposed.

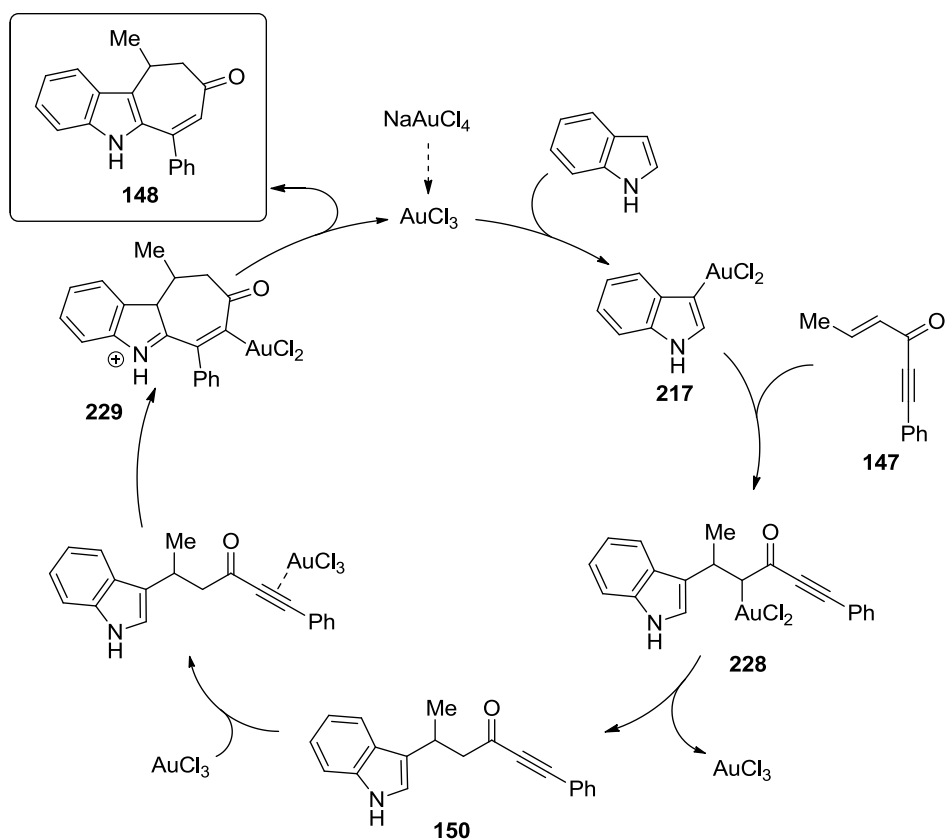


Figure 16 – Tentative mechanism for the double alkylation of indole by enynes

C-3 auration of indole by gold(III) chloride provides the reactive intermediate **217**, which is capable of undergoing cuprate-type addition to enyne **147**. Protonation of mono-addition product **228** regenerates the catalyst, which is then capable of alkyne activation. 7-*endo-dig* cyclisation of **150** gives the auranated tricyclic **229**, which can be protonated to afford the tricyclic product **148**.

2.7 Conclusion

A highly efficient Au-catalysed cascade process is presented, offering access to medicinally relevant [6,5,7]-tricyclic indoles. The reaction is operationally simple, allowing for the use of technical grade reagents without the exclusion of water or air.

The generality of our transformation allows for a wide range of indoles to be utilised, including indoles bearing electron rich and poor functionality, unprotected hydroxyl groups as well as function handles for late stage elaboration. Cross-coupling of **165** and **166** has shown that it is possible to carry out post-cyclisation functionalization of our reaction products. Due to the structural modularity of our synthesis, a diverse range of enynones have been employed as the double electrophiles in our reaction, with reaction generally proceeding in high yield. It has been shown that enynones bearing alkyl functionality at the alkyne terminus are inferior substrates for the cascade, requiring extended reaction times and higher temperatures to affect annulation.

Whilst undertaking reactions to determine the reaction mechanism, it was found that the addition of stoichiometric quantities of water accelerates the rate of reaction for certain substrates, and in two cases drastically increasing the yield of reaction.

Through a series of deuterium-labelling experiments, it has been shown that auration of indole at C-3 occurs, with cuprate-type addition to the enone responsible for the intermolecular alkylation of indole. Studies to elucidate the mechanism of the intramolecular cyclisation in our system have shown that auration at C-2 of indole is possible when the C-3 position is substituted. It is hypothesised that alkyne activation by Au(III) is in fact the reaction pathway due to the reaction rate of annulation compared to the apparent rate of C-2 auration of indole.

2.8 Future work

A logical continuation of this body of work would be further elaboration of the enynone scaffold. Performing the double alkylation on indole **230** with enynone **147** would allow for the rapid construction of indolo-carboxylic acid **146** analogues.

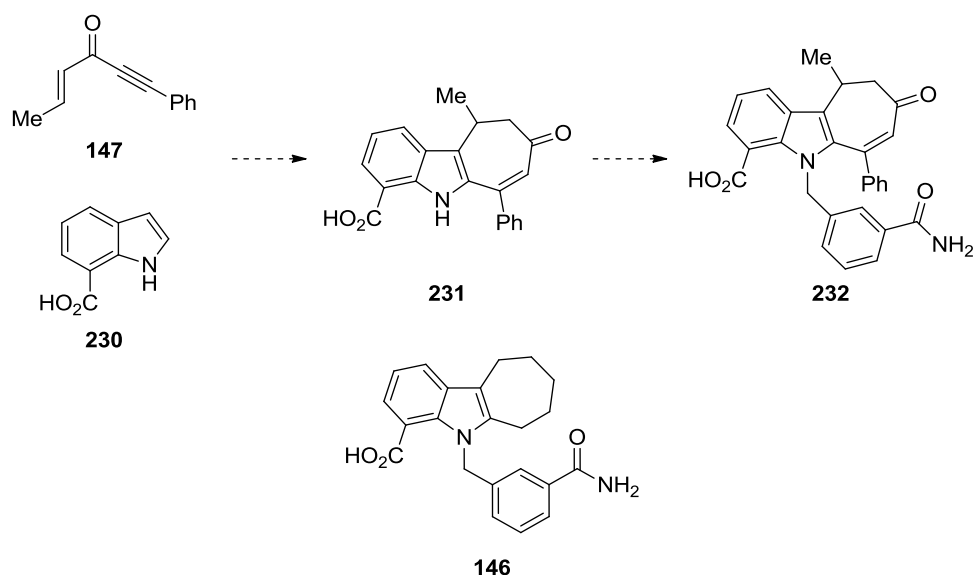


Figure 17 – Possible example of a double alkylation of indole-7-carboxylic acid **230**

To build up further complexity in our products, cyclic enynones of type **233** could be utilised, allowing for the synthesis of tetracyclic scaffolds.

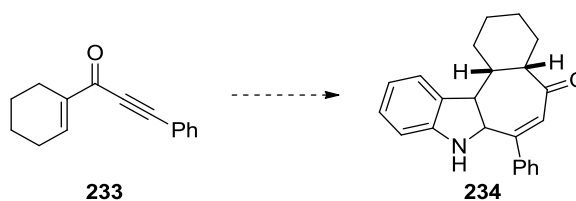


Figure 18 – Potential tetracycle **233** formation from cyclic enynone **233**

Besides a more comprehensive substrate scope study, an extension of the nucleophile scope could examine the application of use alternative electron rich heteroaromatics such as *N*-methylpyrrole **235**, 1,2,3-trimethylpyrrole **236** and benzofuran **237**.

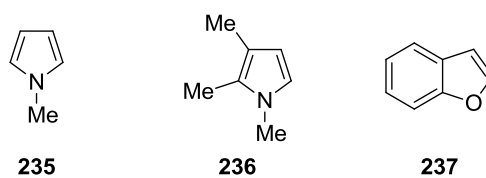


Figure 19 – Examples of alternative conjugate addition donors, 235-237

3. GOLD CATALYSED REARRANGEMENT OF YNAMIDO ESTERS

3.1 Background

3.1.1 Alkynes, ynamines and ynamides

Alkynes are versatile synthetic motifs, made up of a linear C-C triple bond; as such they are generally considered electron-rich and are able to undergo electrophilic addition reactions.

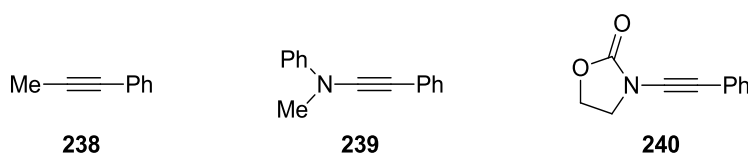


Figure 20 – Example of an alkyne **238**, ynamine **239** and ynamide **240**

A useful sub-group of alkynes are those containing terminal heteroatom substituents, as when utilised in reactions traditionally carried out by alkynes, they allow for the facile incorporation of heteroatom containing groups into the reaction products, which allows for subsequent transformations.¹⁴¹ Nitrogen imparts a strong electronic bias to the alkyne due to the ability of nitrogen to donate its lone pair into the alkynyl moiety, allowing for highly regioselective transformations.¹⁴²

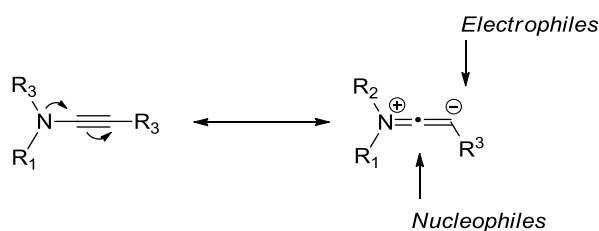
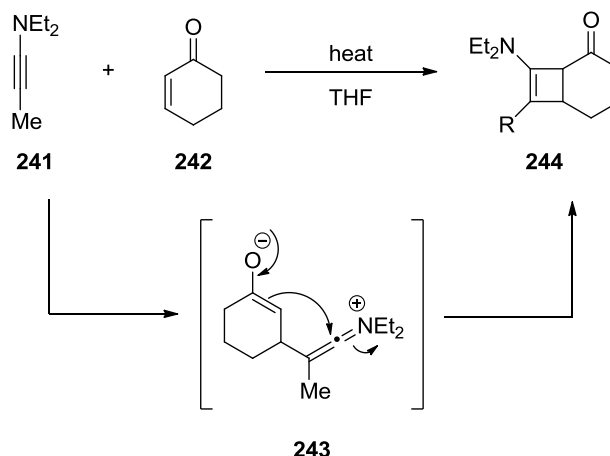


Figure 21 – Electronic bias of ynamides

The use of ynamines in organic synthesis has been widely studied, with cycloaddition reactions having gained the most attention. Ficini *et al.* reported the formal [2+2] cycloaddition of ynamine **241** to cyclohexenone **242** to afford cyclobutenamine **244**.¹⁴³



Scheme 71 – Cycloaddition of ynamine 241 with cyclohexenone 242

Although ynamines offer expedient routes to complex products, their inherent reactivity and sensitivity to hydrolysis have restricted their applications. To increase the stability of ynamines, without significantly diminishing their reactivity, electron-withdrawing groups have been appended to the nitrogen atom. Ynamides reduce the electron donating ability of the nitrogen atom, by incorporating the nitrogen in an electron-withdrawing group such as oxazolidinones, sulfonamides, carbamates and lactams.

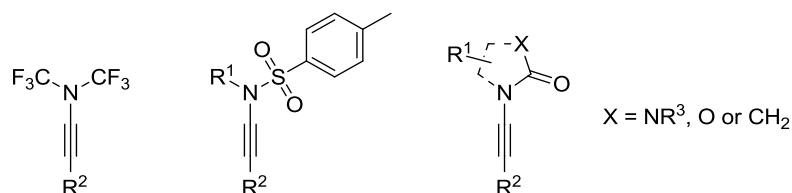


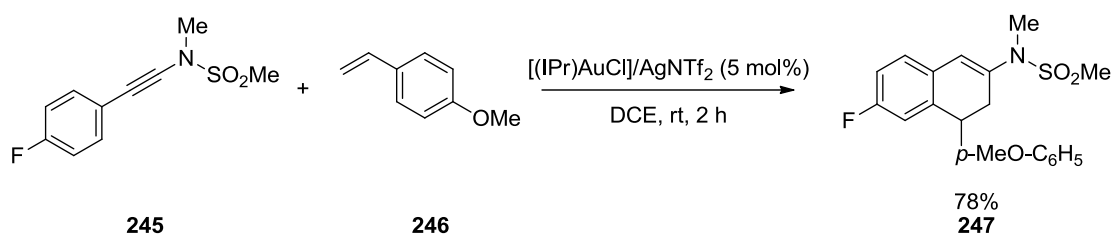
Figure 22 – Representative structures of a range of ynamides

This modification increases their stability and therefore increases the potential applications of ynamides in organic synthesis. A number of in-depth reviews of ynamide chemistry have been published, however only selected gold-catalysed examples will be discussed here.^{141, 144}

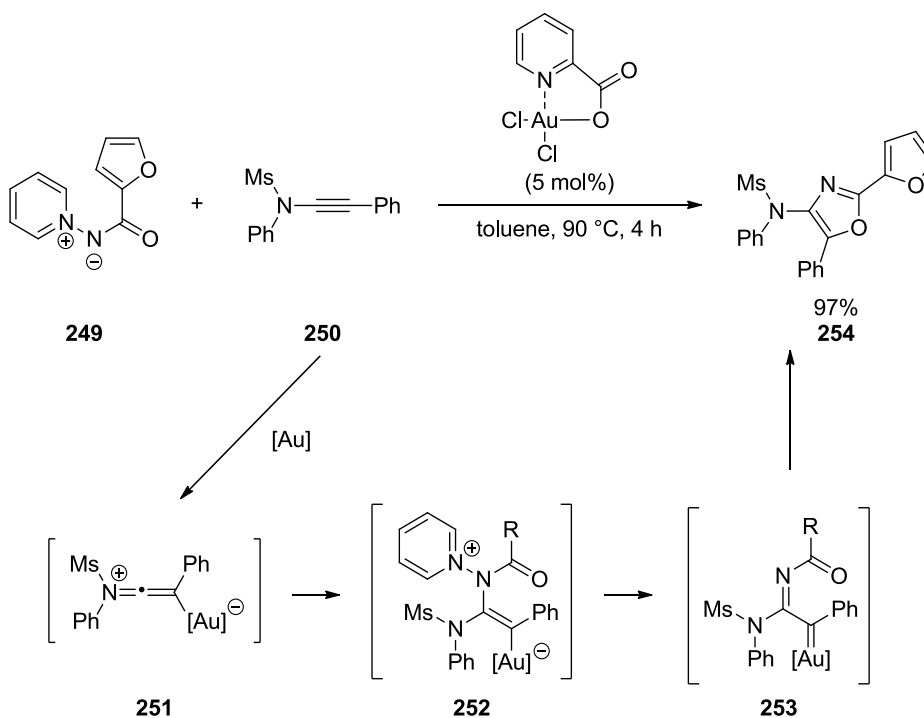
3.1.2 Gold-catalysed reactions of ynamides

Cycloaddition

The vast majority of ynamide chemistry has been focused around cycloadditions, forming multiple C-C bonds in one step, allowing access to complex ring scaffolds.

Scheme 72 – Gold-catalysed [4+2] cycloaddition of ynamide **245**

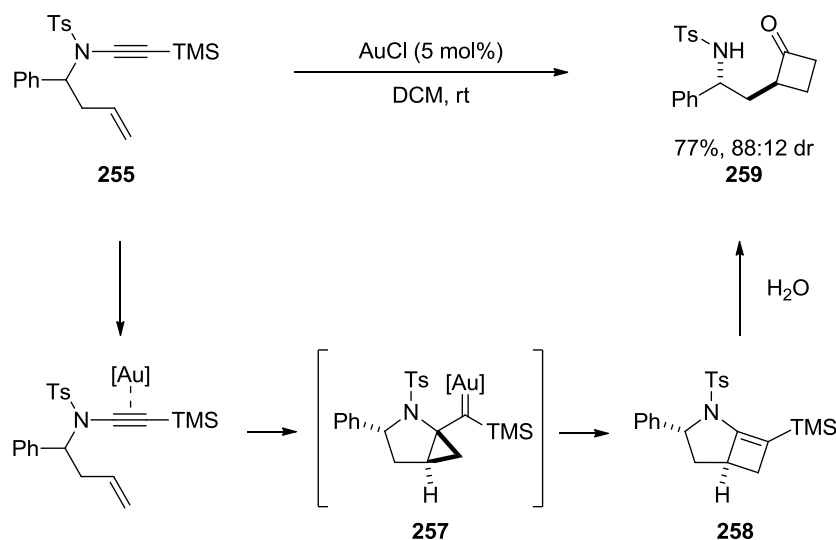
Although typically using ruthenium complexes to affect cyclisation, gold has been shown to be an excellent catalyst for such transformations, with aryl-ynamide **245** undergoing a formal [4+2] cycloaddition with alkene **246** under gold-catalysed conditions.¹⁴⁵

Scheme 73 – Formal [3+2] cycloaddition of ynamide **250** with *N*-ylide **249**

Davies *et al.* envisaged that conjugated *N*-ylides would not only be able to add to ynamides under gold-catalysed conditions, but also quench any auated intermediate, providing formal [3+2] cycloaddition products.¹⁴⁶ Following auration of ynamide **250**, addition of *N*-ylide **249** occurs at the carbon α - to nitrogen of **251**, quenching the positive charge on nitrogen. Elimination of pyridine affords the gold-carbenoid intermediate **253**, which undergoes cyclisation and demetalation to afford oxazole **254**.

Cycloisomerisation

Analogous to the reactivity of enynes discussed previously, 1,6 ene-ynamides are capable of being activated by gold (I) catalysis.¹⁴⁷

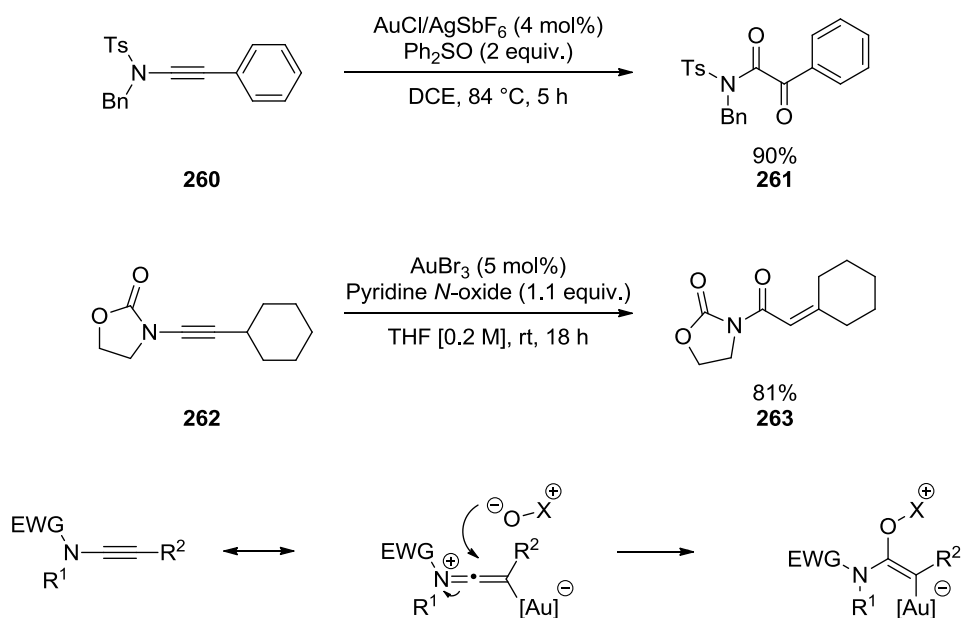


Scheme 74 - 1,6 Ene-ynamide **255** cycloisomerisation

Due to the inherent reactivity imparted by nitrogen, the product expected from the cycloisomerisation, **258**, is not isolable following flash chromatography. Desilylation and hydrolysis occur rapidly, giving amino cyclobutanone **259** as the sole product.

Oxidation

Two complimentary procedures have been developed for the oxidation of ynamides that utilise substrate control to form α -keto imides¹⁴⁸ and α,β -unsaturated imides¹⁴⁹ respectively.



Scheme 75 – Regioselective oxidation of ynamides **260 and **262** under gold-catalysed conditions**

Following auration of the respective ynamides, nucleophilic attack by the external oxidant occurs. Expulsion of the cationic group, diphenyl sulphide and pyridine respectively, gives a gold carbenoid. In the case of phenyl ynamide **260**, a second equivalent of oxidant can be incorporated giving α -keto imide **261**. Conversely, when cyclohexyl ynamide **262** is used, 1,2-insertion occurs to give the unsaturated product **263**.

3.2 Concept development

Propargylic esters have proved to be valuable organic building blocks in the field of metal catalysed transformations, particularly in the field of gold catalysis.¹⁵⁰ Subjected to gold catalysis, these molecules undergo either 1,2- or 1,3- acyl migration, leading to either [Au]-carbene complex or allene seen in Figure 21.¹⁵¹ There are many factors which can influence which of these intermediates is formed within a reaction, including the propargylic, acetylenic and the acyl substituent, however no general trend has been observed.¹⁵² Interestingly, research by Cavallo *et al.* has shown that both the carbene and allene can be easily interconverted, indicating that substrate substitution will influence which of these intermediates react further.¹⁵¹

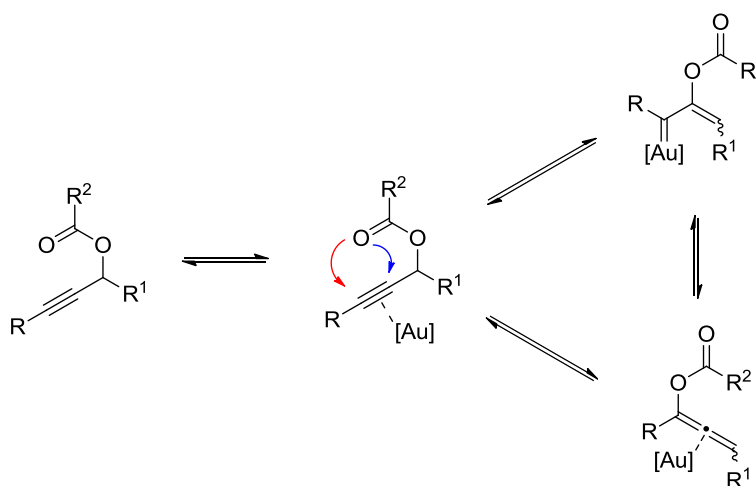


Figure 23 – Potential reaction pathways for the gold-catalysed acyl migration of propargyl esters

These intermediates are highly reactive and allow for further transformations to be conducted. We envisaged that the gold catalysed rearrangement of ynamido esters would allow for regioselective 1,3-acyl migration due to the electronic bias of the ynamide. This reaction would provide acyloxy-allenamides seen in Figure 22, which are previously unreported.

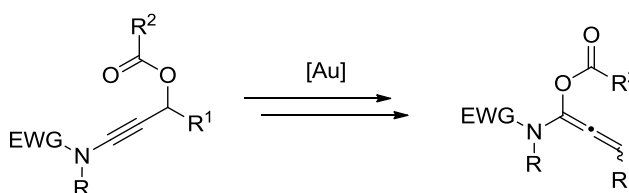


Figure 24 – Hypothesised allenamide product from the gold-catalysed reaction of ynamido esters.

3.2.1 Retrosynthetic analysis

In order to evaluate the viability of a gold-catalysed ynamide rearrangement, synthesis of a model ynamido ester was required. Performing a retrosynthetic analysis of **264**, it can be envisaged that ynamido alcohol **266** would be a suitable precursor, synthesised by simple ester formation. In turn, ynamido alcohol **266** should be readily accessible from the commercially available alcohol **267**.

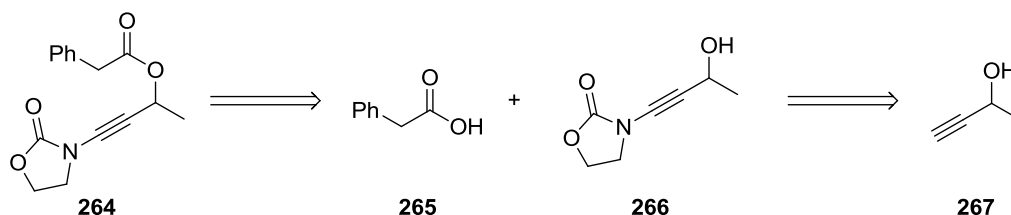
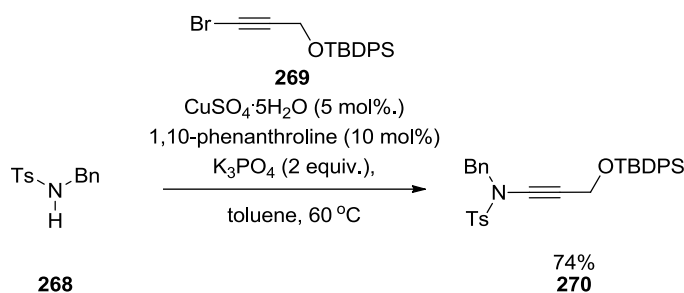


Figure 25 – Retrosynthetic analysis of ynamido ester **264**

Hsung *et al.* have reported a general synthesis of ynamides, with primary ynamido propargylic alcohols being synthesized in good yield.¹⁵³ This method involves the copper-catalysed coupling between a sulfonamide and bromoalkyne.

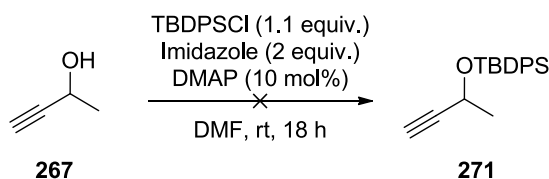


Scheme 76 – Hsung's synthesis of protected ynamido alcohol **269**

This method appears to be a viable route for the synthesis of the required synthetic intermediate, with bromoalkyne **272** readily formed *via* the NBS-promoted bromination of secondary propargylic alcohol **271**.

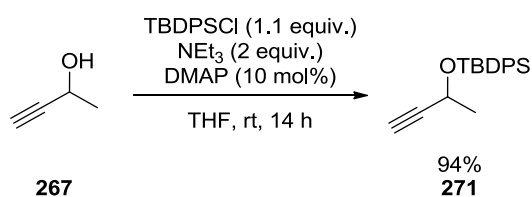
3.3 Synthesis of model substrate

With literature precedence for the formation of ynamido alcohol **266**, silylation of propargylic alcohol **267** was first required. Unfortunately silylation under standard reaction conditions failed to provide any product, with alcohol **267** being returned quantitatively.¹⁵⁴



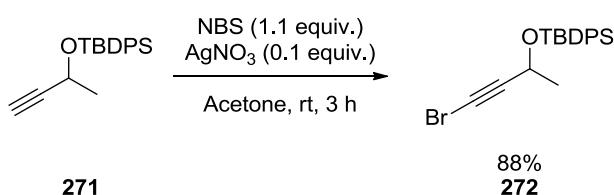
Scheme 77 – Failed hydroxyl protection

After further investigation, a set of alternative conditions were discovered for the silylation step, using triethylamine as the base, with these conditions providing the protected alcohol **271** in high yield.¹³⁷



Scheme 78 – Synthesis of protected alcohol **271**

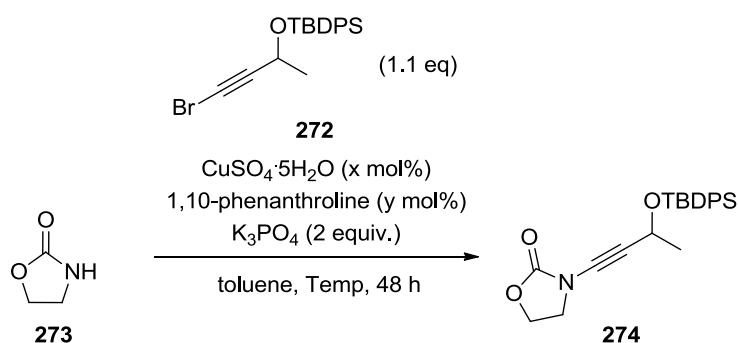
With the protected alcohol **271** in hand, bromination was attempted using Barbazanges's conditions for the bromination of TMS-acetylene.¹⁵⁵ It was found that recrystallisation of *N*-bromosuccinimide prior to use in the reaction, increased the yield of bromoalkyne **272** from 81% to 88%. Favourably, both this and the previous reaction can be carried out on large scale (~50 grams) without any loss of yield.



Scheme 79 – NBS promoted bromination of terminal alkyne **271**

With the synthesis of the bromo-alkyne **272** completed, it was now necessary to couple this product with oxazolidin-2-one **273** to afford ynamide **274**. It was found that following the procedure laid out by Hsung failed to give satisfactory yields (Table 10, entry 1), with large quantities of starting material remaining even after 48 hours.¹⁵⁶ An investigation into the reaction conditions was therefore undertaken in an attempt to improve on the literature conditions.

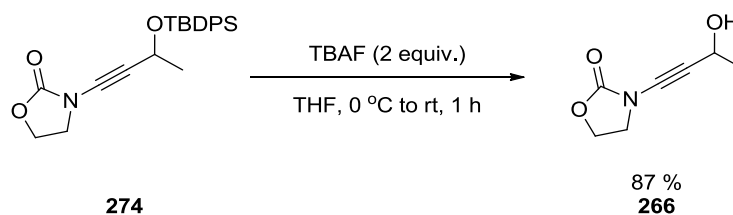
Table 10 – Ynamide formation optimisation



Entry	x [mol%]	y [mol%]	Temp [°C]	Yield [%]
1	5	10	60	42
2	20	40	60	51
3	20	40	110	64
4	40	80	110	65
5	100	200	110	63

At 60 °C, increasing the catalyst loading provided marginally increased reaction yield (Entry 2), however, when increased temperatures were employed the yield was again improved (Entry 3). The ability to isolate and recycle any remaining starting material from this reaction compensates for the lower reaction yields.

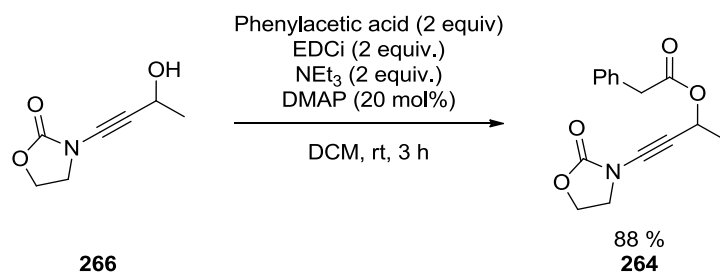
Fluoride promoted deprotection of ynamide **274** was then carried out to allow for the subsequent esterification of alcohol **266**.¹⁵⁵



Scheme 80 – Fluoride promoted deprotection of ynamido alcohol **266**

It became apparent that the temperature at which the TBAF is added to the reaction is vital, with addition at ambient temperature only providing a 65 %. When the reaction was carried out at 0 °C, the fluoride-promoted deprotection gave alcohol **266** in 87 % yield after just one hour.

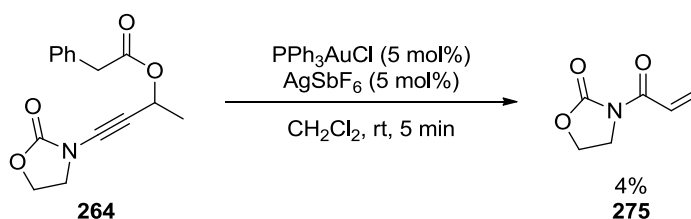
Although many methods of esterification would be appropriate for the formation of **264**, the by-products of EDCi promoted couplings can conveniently be removed from the reaction mixture through weak acid-base extraction, with products often needing no further purification. Coupling of alcohol **266** and phenylacetic acid **265** under conditions developed in the Carbery group gave the required ynamido ester in good yield after recrystallisation of the crude reaction mixture.¹⁵⁷



Scheme 81 - Carbodiimide promoted esterification of ynamido alcohol **266**

3.4 Reaction optimisation

With the model substrate in hand, we attempted the formal [3,3]-rearrangement of ynamido ester **264**. It was decided that a cationic gold(I) catalyst would be optimum for the reaction, as demonstrated by the C-O bond forming ability of this catalyst system previously discussed.^{158, 159}



Scheme 82 – Initial reaction

Upon addition of the catalysts, instant consumption of the starting material was witnessed, with TLC analysis of the crude reaction mixture showing three products. Trace amounts of **275** were isolated from the crude reaction mixture, potentially formed by the hydrolysis of the hypothesised allenamide intermediate **276**.

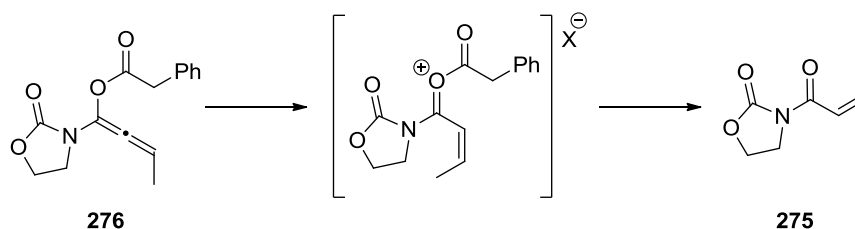


Figure 26 – Hypothesised mechanism of hydrolysis towards the formation of **275**

Although one product from the reaction had been isolated, TLC analysis of the crude reaction mixture had shown the formation of two additional products. Attempts to isolate these products by flash chromatography proved unsuccessful with no mass being returned even following a methanolic flush. Efforts to isolate these additional reaction products by alumina chromatography proved equally fruitless, with recrystallisation unfeasible due to the lack of crystallinity of the products.

It was hypothesised that the desired allenamide **276** was being formed as part of the reaction, but due to its inherent reactivity, it is possible that the cationic gold(I) complex was capable of catalysing subsequent reactions of this intermediate.

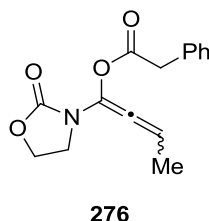
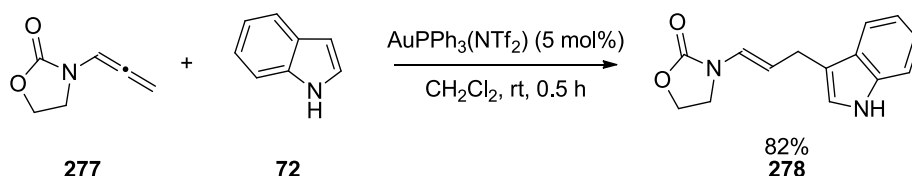


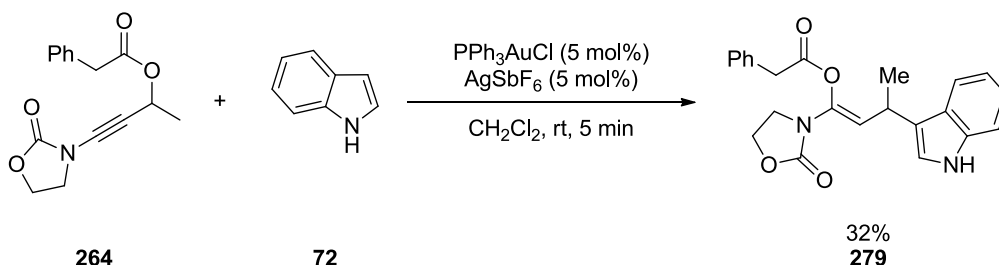
Figure 27 – Proposed reaction intermediate

Kimber *et al.* have shown it is possible to use cationic gold(I) complexes to catalyse the addition of a range of nucleophiles onto simple allenamides.¹⁶⁰



Scheme 83 – Gold-catalysed nucleophilic addition to allenamide **277**

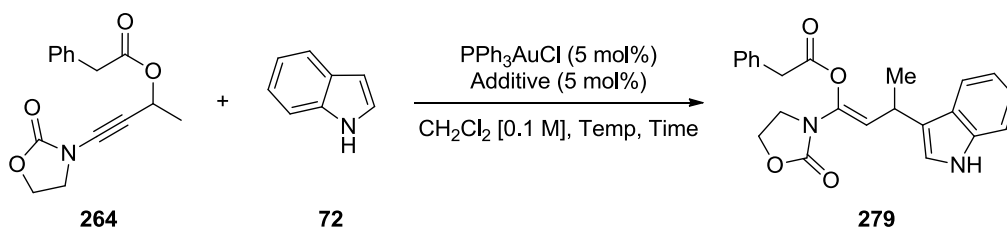
We believed it may be possible to carry out a tandem gold(I)-catalysed transformation, with nucleophilic addition to allenamide **275** following the formal [3,3]-rearrangement. Interception of allenamide **275** with indole **72** should reduce the reactivity of the products, allowing for purification of the reaction products, with the advantage of incorporating the indole nucleus into our scaffold.



Scheme 84 – Tandem rearrangement and nucleophilic addition to afford enamide **279**

The tandem process gave enamide **279** as a single regioisomer in modest yield, confirming that allenamide **276** is indeed formed in our reaction. Although the nucleophilic addition of indole does occur, a large quantity of the starting material is still converted into the two unidentified products. To increase the yield of enamide **279**, a number of reaction variables were investigated.

Table 11 – Reaction optimisation



Entry	Additive	Temp [°C]	Time [min]	Yield [%]
1	AgSbF_6	25	5	32
2	AgPF_6	25	5	59
3	AgPF_6	0	20	62
4	$\text{AgPF}_6^{[\text{a}]}$	0	20	61
5	AgPF_6	-30	45	63
6	AgPF_6	-78	180	0
7	AgPF_6	-30 to 25	45	52
8	$\text{AgPF}_6^{[\text{b}]}$	-30	45	70
9	$\text{AgPF}_6^{[\text{b}], [\text{c}]}$	-30	45	93

[a] concentration = [0.2 M], [b] catalysts added portionwise, [c] fresh AgPF_6 used

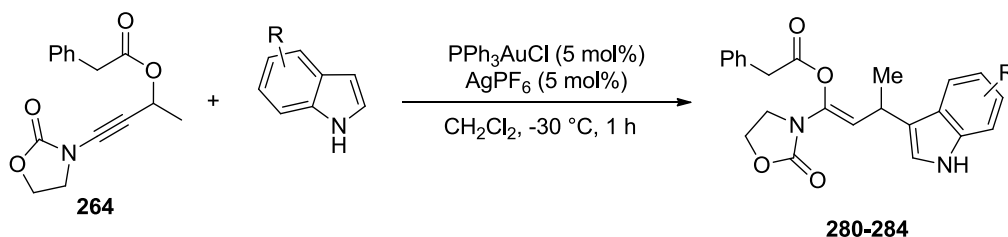
An improvement of yield is witnessed on changing to silver hexafluorophosphate (Table 11, entry 2), although the two unidentified products were still present. In order to slow the formation of the side products, the reaction was cooled to 0 °C, however no appreciable increase in yield was observed (entry 3). Cooling the reaction to -30 °C provided no increase in yield, however, no side products were formed, with the remaining mass returned as starting material (entry 5). Further cooling of the reaction resulted in no reaction due to catalyst insolubility (entry 6). As starting material remained on reaction at -30 °C, a reaction was initiated at low temperature and subsequently warmed to room temperature. Although all starting ynamide **264** was

consumed, a decrease in yield was observed, with the two side products being formed (entry 7). It was noted that at -30 °C, the catalyst was sparingly soluble in the reaction mixture, potentially accounting for the return of starting material at this temperature. Addition of the catalyst portionwise to counteract this observation gave an increase in yield to 70% (entry 8). It is worth noting at this point that silver hexafluorophosphate is highly hygroscopic, rapidly becoming liquid under atmospheric conditions. When a fresh batch of the silver hexafluorophosphate was used under our optimised conditions a dramatic increase in yield of enamide **279** was witnessed.

3.5 Nucleophile scope

With optimised conditions discovered for the tandem gold-catalysed reaction of ynamido esters and indole, it was decided to assess the generality of this process. To this end, a range of functionalised indoles were reacted with ynamide **264**.

Table 12 – Indole scope



Entry	Indole	Product	Yield [%]
1	5-Me	280	89
2	5-I	281	92
3	5-F	282	99
4	5-CO ₂ Me ^[a]	283	53
5	6-OMe	284	92

Electron neutral indoles perform the addition well, proceeding in high yield (Table 12, entries 1-3), with 5-iodo indole allowing for further elaboration of the reaction product **281** (entry 2). Electron poor indoles also undergo the reaction, affording **283**, however, reaction yield is reduced. The decrease in yield may be due to the decreased nucleophilicity of the indole slowing the addition reaction, allowing for the formation of

side-products (entry 4). The reaction is also tolerant of alternate indole substitution, as demonstrated by the formation of **284**.

Although the reaction affords a single geometrical isomer, analysis of the reaction products by ^1H NMR did not provide sufficient information to determine the absolute alkene geometry of the product. Enamide **281** was found to be crystalline, with single crystal X-ray diffraction analysis of the product showing the formation of the (Z)-alkene.

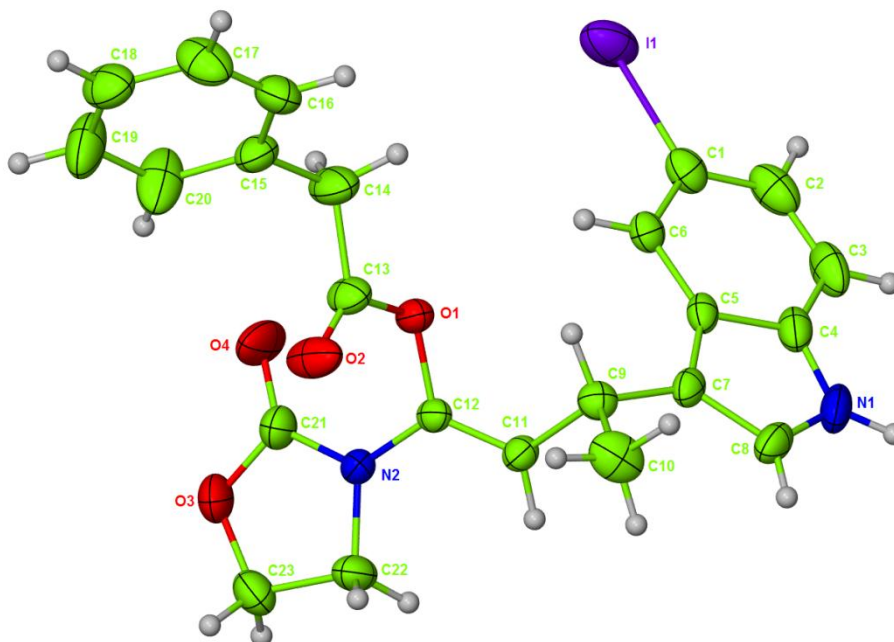
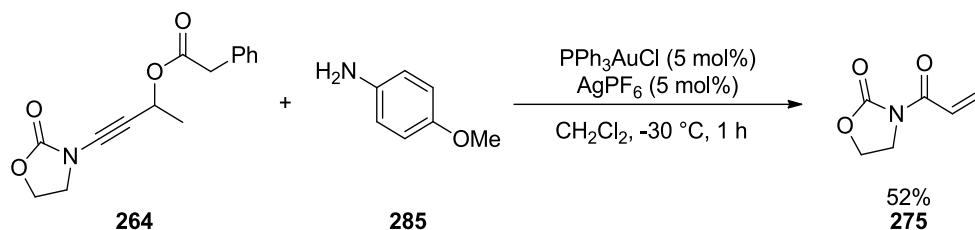


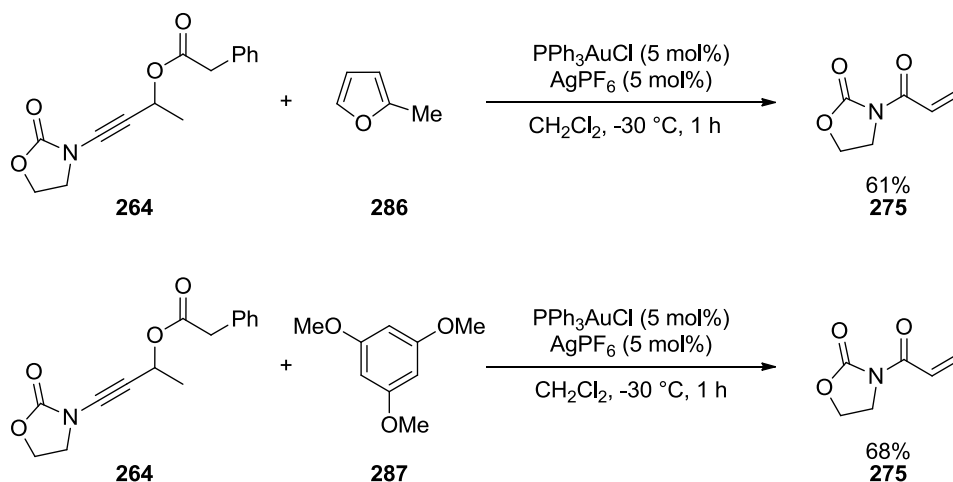
Figure 28 - XRD analysis of of tricycle 281

3.5.1 Alternative nucleophiles

Kimber *et al.* have shown it is possible to utilise a range of nucleophiles for the addition to allenamides, including electron-rich aromatics, anilines, *N*-methyl pyrrole and 2-methyl furan.¹⁶⁰ In order to assess the scope of our reaction with regards to the nucleophilic addition, a range of nucleophiles were employed in our tandem process.

Scheme 85 – Attempted addition of 4-methoxyaniline **285** to ynamido ester **264**

Although Kimber has shown aniline can undergo addition to allenamides (Scheme 83), when subjected to our optimised reaction conditions, none of the desired product was observed, with the reaction exclusively providing the hydrolysis product **275**. This may indicate that 4-methoxyaniline is not nucleophilic enough to trap our allenamide before it undergoes further transformations. This mirrors the findings seen when using methyl-indole-5-carboxylate (Table 12, entry 4), as although the desired product was formed, substantial quantities of by-product were also formed, indicating that reaction success is highly dependent on the nucleophilicity of our nucleophile.

Scheme 86 – Alternative nucleophiles afford exclusively hydrolysis product **275**

Both 2-methyl furan **286** and 1,3,5-trimethoxybenzene **287** gave the hydrolysis product **275** seen in previous reactions, suggesting that they may also not be nucleophilic enough to intercept allenamide **276** before it can decompose.

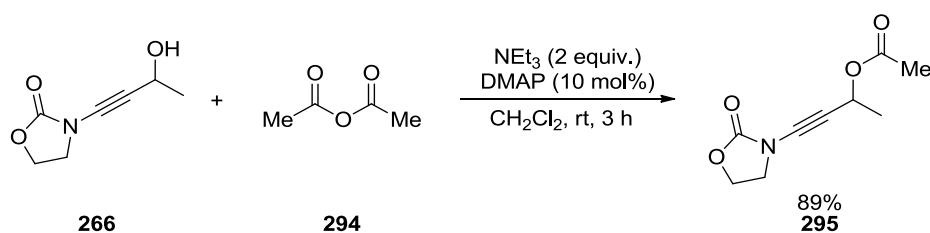
3.6 Ynamido ester scope

Having demonstrated the scope of reaction with regards to the nucleophile employed, a range of ynamido esters were synthesised to determine the scope of the gold-catalysed [3,3]-rearrangement.

Table 13 – Carbodiimide promoted esterifications

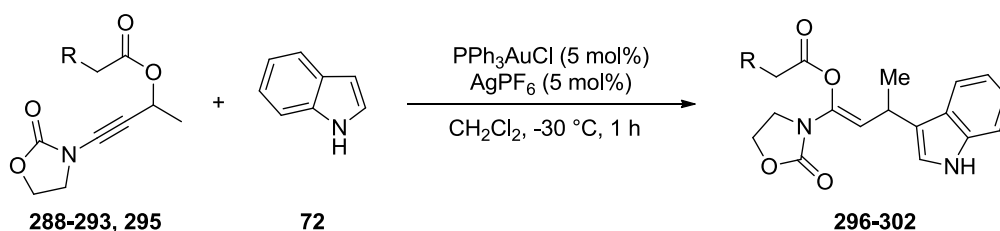
Entry	R	Product	Yield [%]
1	4-MeC ₆ H ₄	288	74
2	4-OMeC ₆ H ₄	289	79
3	4-NMe ₂ C ₆ H ₄	290	68
4	4-FC ₆ H ₄	291	57
5	4-IC ₆ H ₄	292	71
6	3,4-(O ₂ CH ₂)C ₆ H ₃	293	60

Utilising the same methodology as previously employed in the synthesis of our test substrate, a range of aromatic esters were synthesised to explore the electronic limitations of the reaction (Table 13). Electron rich, neutral and poor substrates were prepared by carbodiimide promoted esterification, in an aim to probe the electronic requirements of our reaction. An acetate ester analogue **295** was prepared *via* an alternative method, with a view to expanding the reaction scope, by incorporation of an alkyl ester.¹⁶¹

Scheme 87 – Acetate ester **295** synthesis

With the required substrates in hand, the scope of the ynamido ester rearrangement was explored using our optimised conditions.

Table 14 – Indole scope



Entry	Substrate	R	Product	Yield [%]
1	288	4-MeC ₆ H ₄	296	85
2	289	4-OMeC ₆ H ₄	297	74
3	290	4-NMe ₂ C ₆ H ₄	298	87
4	291	4-FC ₆ H ₄	299	79
5	292	4-IC ₆ H ₄	300	92
6	293	3,4-(O ₂ CH ₂)C ₆ H ₃	301	56
7	295	H	302	89

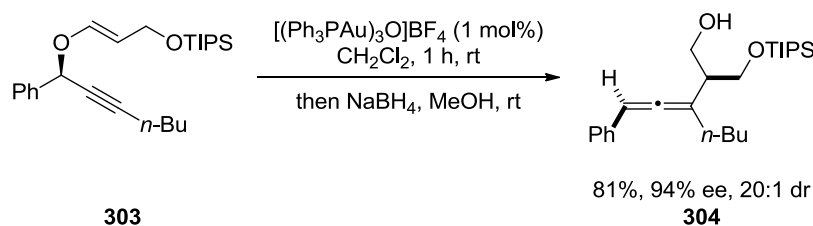
As can be seen the reaction tolerates electron rich and neutral substrates, with methoxy- and dimethylamino- substrates reacting well (Table 14, entries 2-3). Halogenated substrates also smoothly undergo rearrangement and nucleophilic addition (entries 4-5), with **300** allowing for future functionalisation of the reaction products. When piperonylic acid derived substrate **293** is used the yield is lowered (entry 6), this may be due to the addition of steric bulk in the *meta*-position. Alkyl ester **295** was also capable

of undergoing the [3,3]-rearrangement, affording **302** in excellent yield, demonstrating that phenylacetic esters are not necessary for reaction success.

3.6.1 Chirality transfer

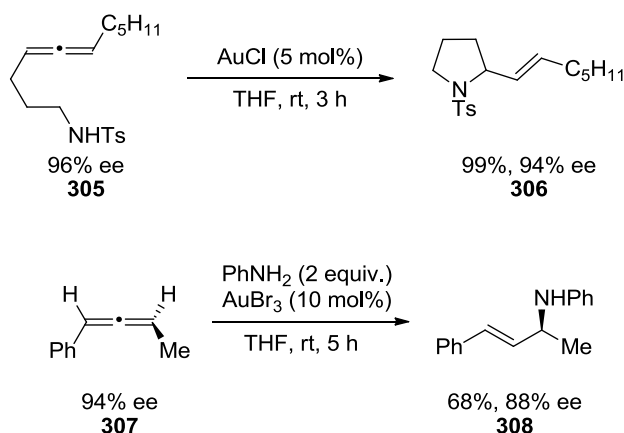
Many catalytic methods exist for the enantioselective formation of complex molecules, many of which rely on the use of chiral ligands to induce chirality in the final product. An alternative method for the formation of chiral molecules involves the transfer of chirality from a substrate through to the desired product.

Due to their availability, and ability to be prepared with high enantioselectivity, chiral propargylic alcohols have garnered much attention in gold-promoted asymmetric transformations.¹⁵⁸ Toste *et al.* have demonstrated the gold(I)-catalysed [3,3]-Claisen rearrangement of **303** to give homoallenic alcohol **304** with excellent diastereo- and enantioselectivity.¹⁶²



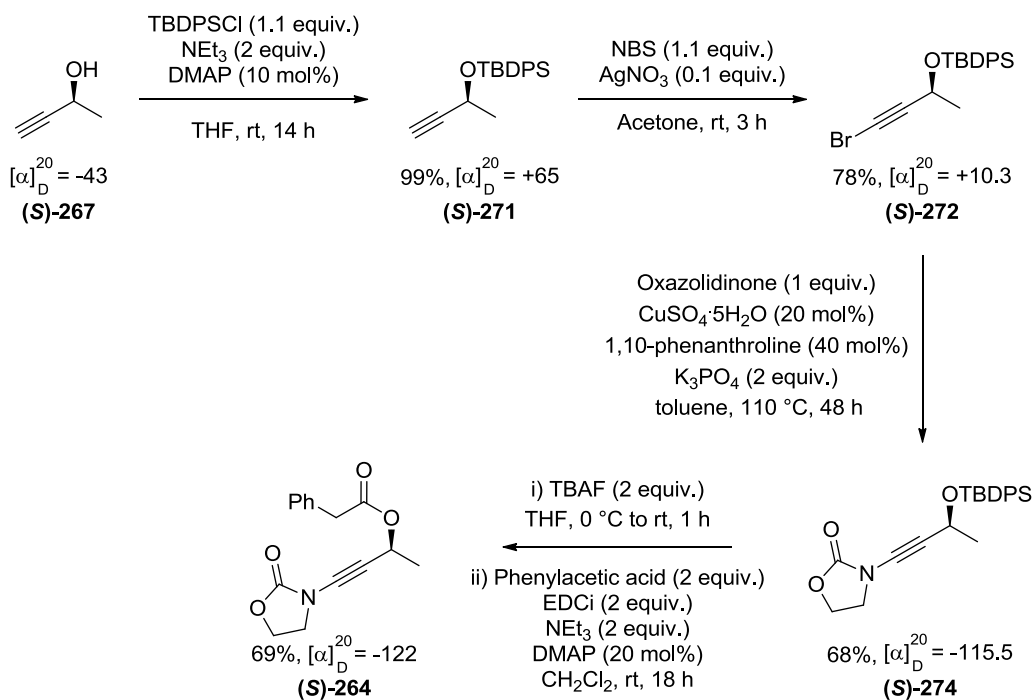
Scheme 88 – Chirality transfer in the Claisen rearrangement of **303**

Allenes have also been shown to be capable of transferring their chirality to their products, with Yamamoto *et al.* reporting both a gold(I)-catalysed intramolecular hydroamination of allenes, and a gold(III)-catalysed intermolecular hydroamination of allenes.¹⁶³



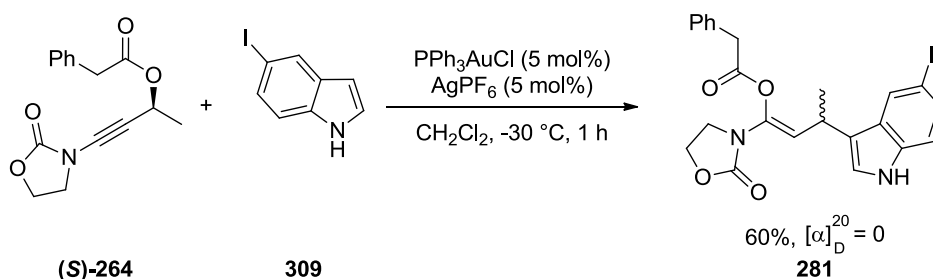
Scheme 89 – Allene chirality transfer

Reactions such as these highlight the ability of gold to catalyse enantioselective [3,3]-rearrangements as well as the ability to promote the nucleophilic addition to allenes with retention of stereochemistry. This led us to hypothesise that, starting from a suitable chiral propargylic alcohol, it may be possible to achieve chirality transfer from an ynamido ester to the intermediate allenamide by formal [3,3]-rearrangement. Subsequent chirality transfer in the nucleophilic addition of indole to allenamide **275** could potentially lead to enantioenriched enamide products.



Scheme 90 – Chiral substrate synthesis

To this end, starting from (*S*)-propargylic alcohol (*S*)-**267**, a chiral substrate was prepared to test this hypothesis. Following our optimised route for the synthesis of ynamido esters, optically active ynamide (*S*)-**264** was prepared in good yield. Subjection of (*S*)-**264** to our optimised reaction conditions afforded enamide **281** in good yield, however no optical activity of the product was witnessed, implying a loss of stereochemical information during our transformation.



Scheme 91 – Attempted chirality transfer in the reaction of (*S*)-**264**

The loss of optical activity in our molecule may be explained by the structure of the intermediate allenamide formed in the reaction. Fensterbank *et al.* have reported that gold allene complexes generally adopt two types of structure, depending on the substituents of the allene.¹⁶⁴

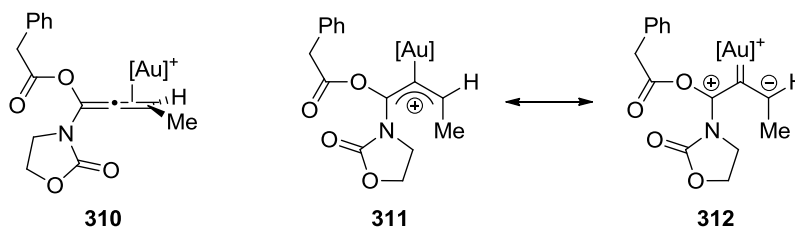
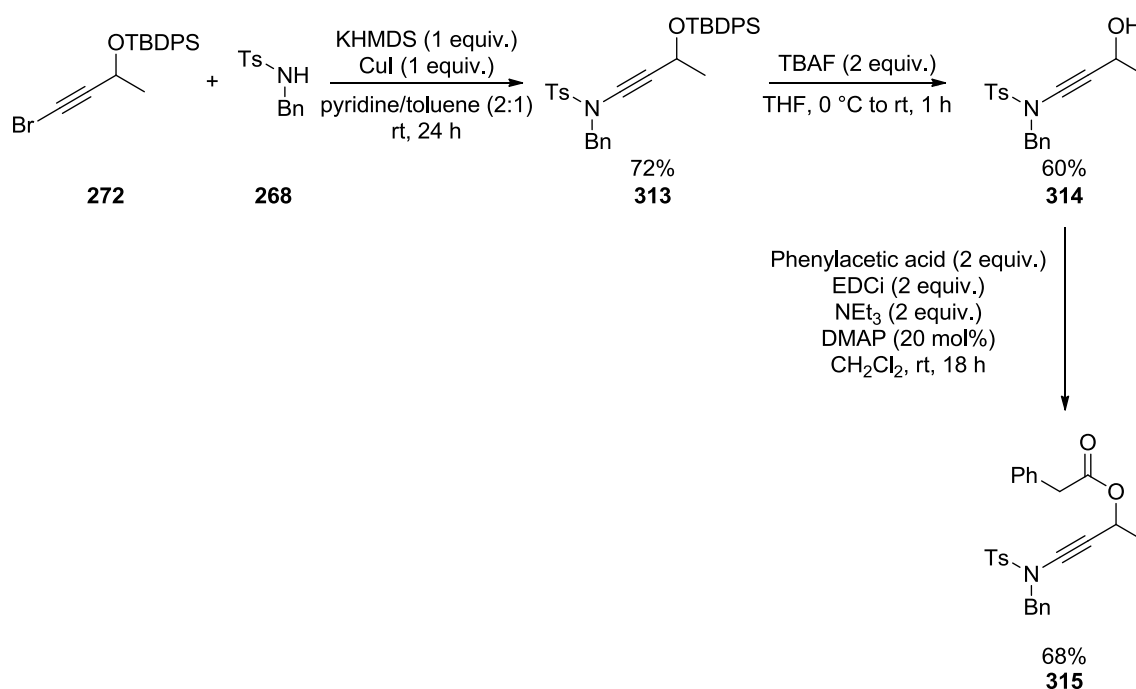


Figure 29 – Potential intermediates of types **310**, **311** and **312** formed during the synthesis of **281**

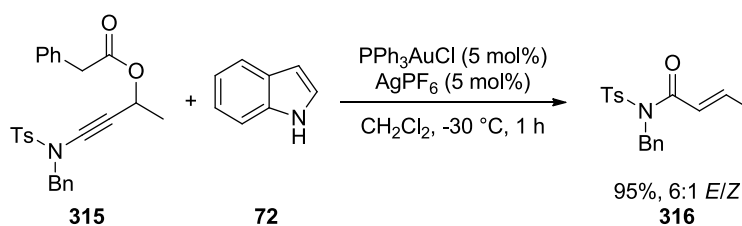
The stereochemical information is retained in species **310**, however, the axial chirality of the allene is lost in species **311** and **312**. It may therefore be possible that although the reaction is concerted, providing a chiral allenamide, the intermediate gold-allene complex is no longer chiral, denying chirality transfer during the intermolecular addition of indole to the allenamide intermediate.

3.6.2 Alternative ynamides

To further expand the scope of our tandem process it was decided to incorporate the nitrogen of our ynamide into a sulfonamide. Sulfonamide containing ynamides have been utilised extensively in ynamide chemistry, and this modification to our substrate would explore the scope of our reaction with regards to the electronic withdrawing nature of our ynamido esters. To this end, sulfonamide **315** was synthesised according to a modified route from the synthesis of the oxazolidinone analogues.

Scheme 92 – Synthesis of sulfonamide **315**

In conjunction with our other studies it was found that although the coupling of oxazolidinone works well under Hsungs' conditions, the coupling of alternative ynamides works with mixed success. Utilising conditions reported by Danheiser *et al.*¹⁶⁵ provides the desired ynamide **313** in good yield, with subsequent deprotection and esterification providing the desired ynamido ester **315**.

Scheme 93 – Hydrolysis during the reaction of **315**

When subjected to our optimised conditions, hydrolysis of sulfonamide **315** occurs to give **316** in near quantitative yield. The formation of **316** implies that the intermediate allenamide formed in this reaction is less reactive towards nucleophilic addition than the oxazolidinone analogue, therefore undergoing hydrolysis before addition of indole can occur.

3.7 Conclusion

A novel gold-catalysed tandem reaction of ynamido esters has been reported, with formal [3,3]-rearrangement of affording allenamide intermediates which undergo nucleophilic addition by indole.

Through the process of reaction optimisation it was found that suppression of side-product formation is essential for reaction success, with allenamide intermediates having to be “trapped” at -30 °C to afford the resultant enamide products in high yields.

A range of functionalised indoles were used for the intermolecular trapping of the reaction intermediates, affording the resultant enamide products in excellent yield, with all products being formed as single regioisomers. The use of 4-methoxyaniline **285**, 2-methylfuran **286** and 1,3,5-trimethoxybenzene **287** all resulted in the formation of an undesired side product, potentially from the hydrolysis of the allenamide intermediate.

An investigation into the ester portion of our molecule revealed the reaction is tolerant of a wide range of phenyl acetate esters, as well as an alkyl variant.

Under our optimised conditions, chiral ynamido ester (*S*)-**264** did not provide chirality transfer through to the product, potentially indicating that the reaction proceeds through intermediates that lead to loss of stereochemical information.

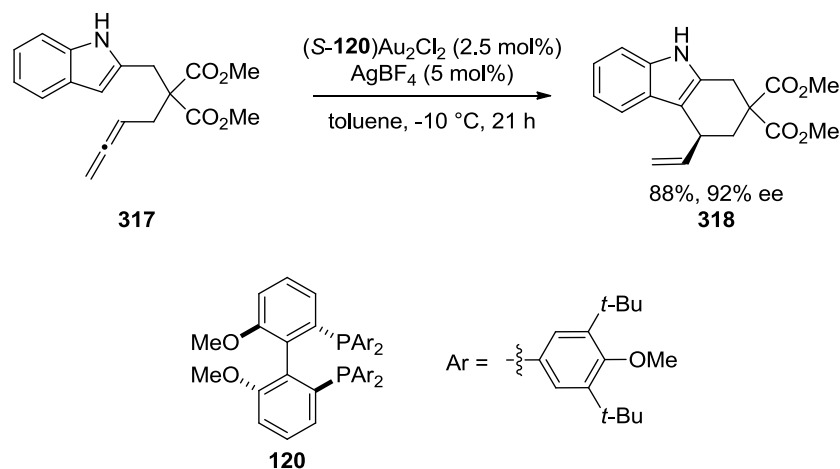
The use of sulfonamide **315** led exclusively to the formation of hydrolysis product **316**, implying that the gold-catalysed nucleophilic addition to the intermediate allenamide is slow compared to the oxazolidinone analogues.

3.8 Future work

A logical extension of this work would be to attempt to halt the formation of the hydrolysis by-products from this reaction, which may be achieved by the use of strictly anhydrous conditions. This has the potential to increase the time for the intermediate allenamide to react with the respective nucleophiles before side-products are formed.

Another area of study might focus on an investigation into the identity of the side-products formed during the reaction at ambient temperature, with an aim to forming products which may be purified by recrystallization to avoid the need for chromatography.

In an attempt to carry out our tandem process enantioselectively, a chiral gold(I) catalyst may be employed. Widenhoefer *et al.* have demonstrated the enantioselective addition of indole to achiral allenes under cationic gold(I)-catalysed conditions.¹⁶⁶



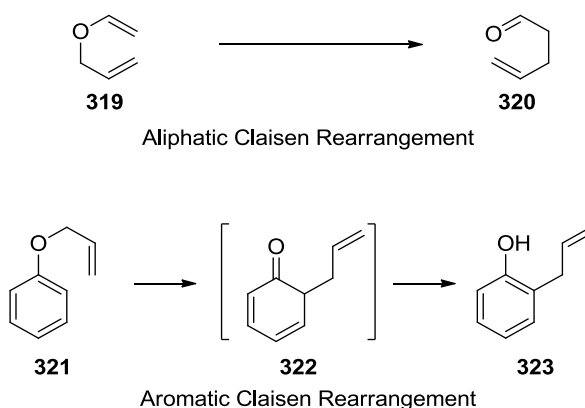
Scheme 94 – Chiral intermolecular nucleophilic addition to allene 317

4. IRELAND CLAISEN REARRANGEMENT OF YNAMIDO ESTERS

4.1 Background

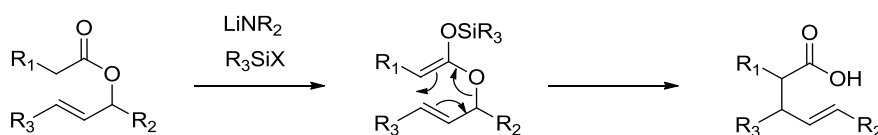
4.1.1 The Ireland-Claisen rearrangement

The first thermal rearrangement of aliphatic and aromatic allyl vinyl ethers was published by Ludwig Claisen in 1912.¹⁶⁷



Scheme 95 – Example of an aliphatic and aromatic Claisen rearrangement

Although examples of ester enolate Claisen reactions had been previously reported, the first by Tseou and Wang in 1937, they suffered from poor yields and the need for forcing reaction conditions.¹⁶⁸ Since that initial discovery in 1937 there were reports of similar rearrangements that made use of sodium metal, sodium hydride and Et_2NMgBr to form the ester enolate.¹⁶⁹



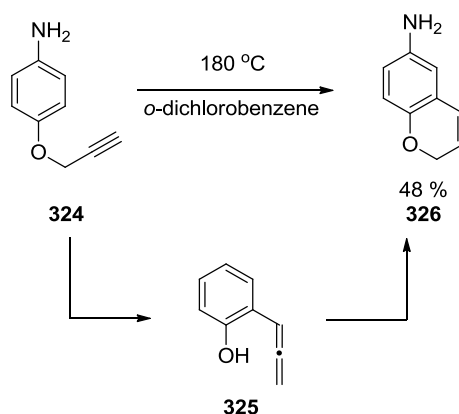
Scheme 96 – Mechanism for the Ireland-Claisen rearrangement

The Ireland-Claisen rearrangement is a variant of the Claisen [3,3]-sigmatropic rearrangement, first reported in 1972 by Robert Ireland, whereby an allylic ester is subjected to a lithium dialkylamine base in the presence of a silylating agent at low temperature.¹⁷⁰ The silyl ketene acetal formed suppresses alternative reaction pathways

such as Claisen-type condensation and decomposition *via* a ketene pathway, allowing the desired [3,3]-sigmatropic rearrangement to occur. γ,δ -Unsaturated carboxylic acid products are afforded following protic workup.

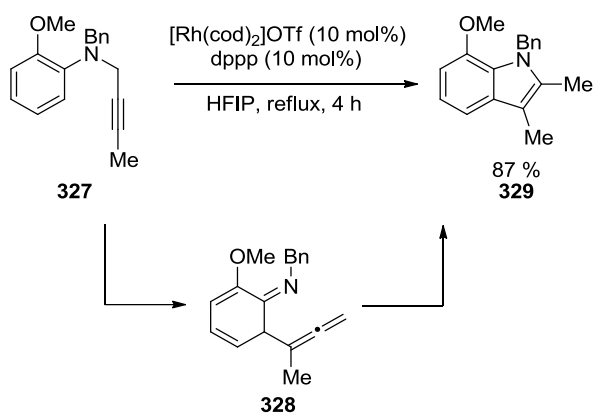
4.1.2 Alkynyl Claisen & Ireland-Claisen Rearrangements

Although not as prominent, the Claisen and Ireland-Claisen rearrangements have also been carried out on substrates containing alkynes. The first example of which was reported by Harfenist in 1971, where 4-(prop-2-ynyloxy)aniline **324** was converted to the corresponding chromene **326**.¹⁷¹ After the initial Claisen rearrangement, rearomatisation affords *o*-allenyl phenol **325**, ring closure then occurs to afford chromene **326**.



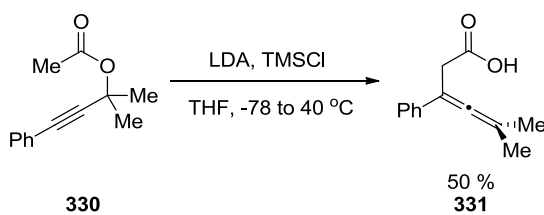
Scheme 97 – First Alkynyl Ireland-Claisen rearrangement

As with the alkene Claisen rearrangement, alternative heteroatoms can be employed in the linker to furnish new products. This was shown by Saito and Hanzawa, in which they replaced the propargyl ether with propargylic anilines.¹⁷² The resultant indoles formed are valuable synthetic building blocks, ubiquitous in the field of natural products and pharmaceutical compounds.



Scheme 98 – Propargyl anilines in the Ireland-Claisen rearrangement

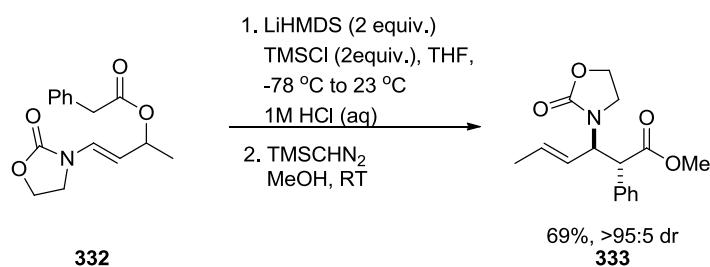
The above reaction was believed to proceed *via* an allene intermediate; however no efforts were made to isolate this intermediate. Studies by Wang *et al.* enabled the isolation of the allene intermediate **331** following an Ireland-Claisen rearrangement.¹⁷³



Scheme 99 – Allene formation in the alkynyl Ireland-Claisen rearrangement

4.2 Concept development

The Carbery group has previously published a novel Ireland-Claisen rearrangement of enamido esters, furnishing β -amino acids in good yield with excellent diastereocontrol.¹⁷⁴



Scheme 100 – Example of an enamide Ireland-Claisen rearrangement

The importance of development of novel methods for the synthesis of β -amino acids is highlighted by their reduced susceptibility to proteolytic degradation when compared to α -amino acids. This has allowed for their incorporation into a number of pharmaceutical molecules, with Taxol **334** showing favourable properties in cancer chemotherapy. The β -amino acid side chain has been shown to be necessary for biological activity.¹⁷⁵

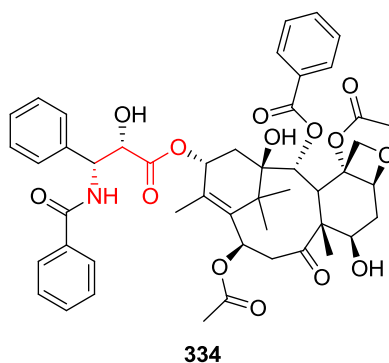
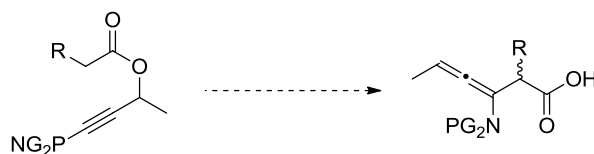


Figure 30 – Taxol **334**, β -amino acid side-chain highlighted in red

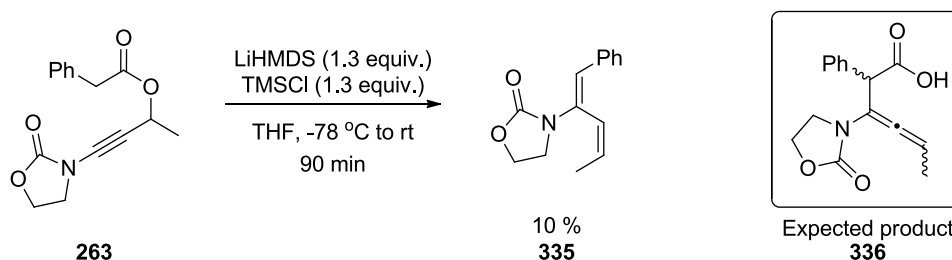
It was hypothesised that ynamido esters may undergo a similar reaction to the enamido Ireland-Claisen rearrangement, yielding 2,3-substituted β -amino acids, containing an allene at the 3-position. This transformation would offer unique functionality for β -amino acids, allowing for further functionalisation of the reaction products.



Scheme 101 – Hypothesised product of an ynamide Ireland-Claisen rearrangement

4.3 Initial investigations

Having a clear rationale for the development of the ynamido Ireland-Claisen rearrangement, the ynamido ester **263**, previously utilised in the gold(I)-catalysed rearrangement of ynamido esters, was selected as a test substrate. **263** was then subjected to the groups' optimised rearrangement procedure in order to evaluate the viability of an ynamido Ireland-Claisen rearrangement.

Scheme 102 – Decarboxylation following the Ireland-Claisen rearrangement of ynamido ester **263**

The hypothesised outcome of this reaction was $\beta^{2,3}$ -amino acid **336**, however, the isolated product was conjugated diene **335**, with the mass balance being made up of starting material **263**. It was postulated that the expected product is being formed in the reaction, but due to the inherent reactivity of the allenamide, decarboxylation occurs post-rearrangement. To account for the observed product, a tentative mechanism is proposed.

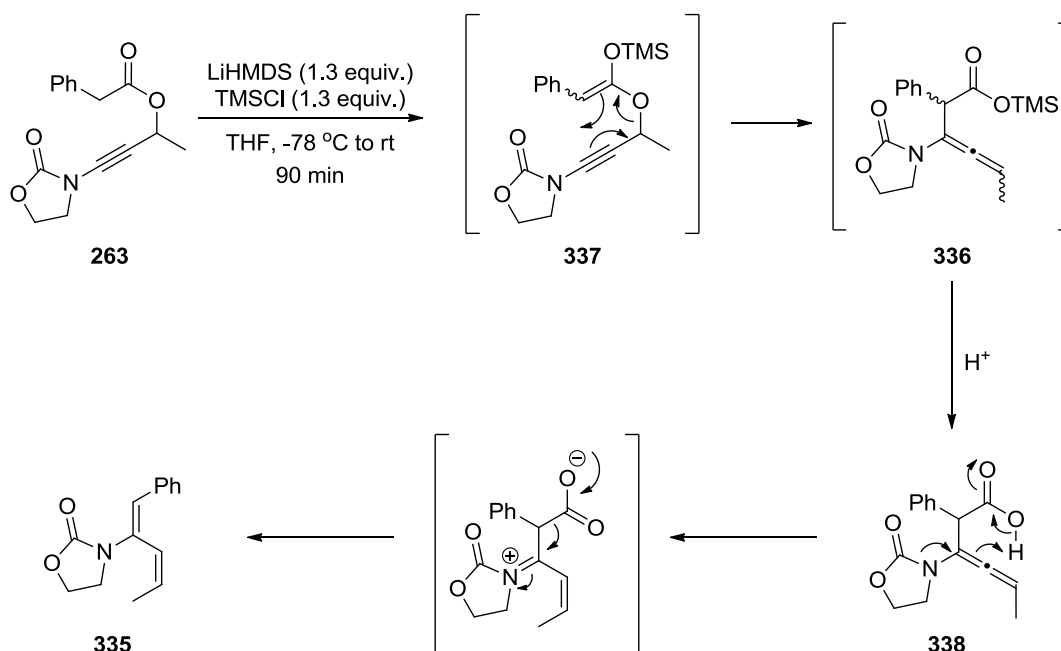
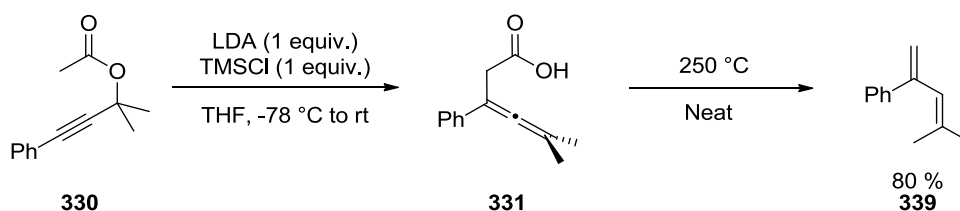


Figure 31 – Proposed mechanism for the formation of amino diene **335**

Following the formation of the silyl ketene acetal **337** and subsequent [3,3] sigmatropic rearrangement, the reaction is quenched with 1M HCl/brine. At this point the trimethylsilyl-oxygen bond is cleaved, giving the free carboxylic acid **338**. The nitrogen can then donate its lone pair into the nitrogen-carbon bond, forming an iminium ion, allowing a [1,5] hydride shift to occur, leading to decarboxylation and quenching of the iminium ion. ¹³C NMR analysis of the crude reaction mixture shows no signals indicative of allene **336**. This is the first example of an ynamido Ireland-Claisen rearrangement, with the intermediate **338** undergoing facile decarboxylation at ambient temperature.

4.3.1 Literature precedence

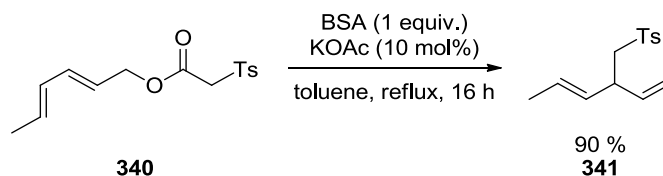
Baldwin *et al.* have shown that under forcing conditions the products of alkynyl Ireland-Claisen rearrangements can undergo decarboxylation.¹⁷⁶



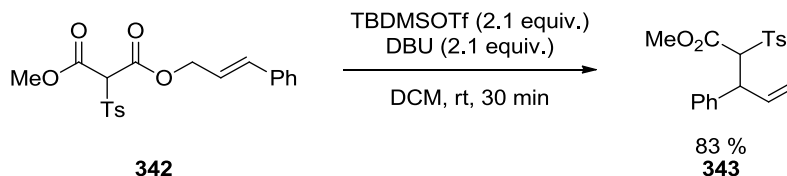
Scheme 103 – First decarboxylative alkynyl Ireland-Claisen rearrangement

This was the first examples of a decarboxylative Ireland-Claisen rearrangement, and it was believed that after the initial [3,3] sigmatropic rearrangement, a [1,5] hydride shift occurred facilitating the decarboxylation. The disadvantage of this reaction is that it has to be carried out under extremely forcing conditions, with temperatures as high as 250 °C being employed in order to give the desired product **339**. Since this initial discovery a handful of decarboxylative Ireland-Claisen variants have been reported.

Craig showed that it was possible to achieve similar results using allylic α -tolylsulfonylacetate esters as the rearrangement substrates; however this still required high temperatures to promote the decarboxylation.¹⁷⁷

Scheme 104 – Ireland-Claisen rearrangement of allylic α -tolylsulfonylacetate ester **340**

When allylic tosylmalonate esters were employed under the same conditions it was found that the reaction could be carried out in dichloromethane at room temperature.¹⁷⁸

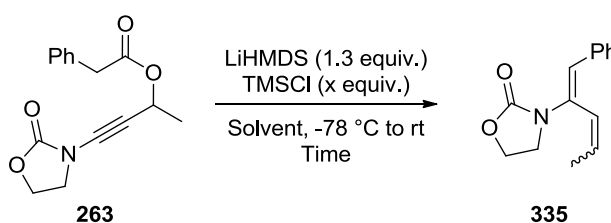
Scheme 105 – Ireland-Claisen rearrangement of allylic tosylmalonate ester **342**

The addition of an extra electron withdrawing group at the enolisable centre is thought to weaken the carbon-carbon bond to the carboxylic acid group after rearrangement therefore making decarboxylation a more facile process.

4.4 Reaction optimisation

With this promising result in hand, it was decided to undertake a series of experiments to optimise the formation of the diene product **335**. As a large quantity of starting material remained after the Ireland-Claisen rearrangement shown in scheme 102 the reaction time was extended to allow for further consumption of starting material.

Table 15 – Initial reaction optimisation



Entry	Solvent	x (equiv.)	Time [h]	Yield [%]	Z/E
1	THF	1.3	24	40	>95:5
2	THF	1.3	48	41	>95:5
3	THF	0	24	0	>95:5
4	Toluene	1.3	24	13	>95:5
5	THF ^[a]	1.3	24	25	>95:5

[a] NaHMDS used

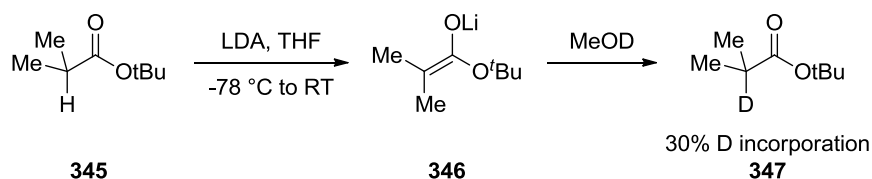
Extended reaction times were found to increase the yield of diene **335** significantly; however extending the reaction timescale to two days offered no further conversion. Omission of chlorotrimethylsilane was detrimental to the reaction, with no product being isolated. Substitution of tetrahydrofuran with toluene diminishes the yield, as does the replacement of LiHMDS with NaHMDS. Sodium may give a less ordered transition state than the lithium base following enolate formation, as it co-ordinates less strongly than lithium, which may impact reaction yield. It should also be noted that the remaining starting material can be reclaimed from the reaction mixture and recycled.

In an effort to increase the yield further, the temperature of deprotonation was explored, with the reactions only being allowed to proceed for 90 minutes to allow for the rapid comparison of conditions.

Table 16 – Investigation into reaction initiation temperature

Entry	Temp (°C)	Yield (%)	Z/E
1	-95	21	>95:5
2	-78	10	>95:5
3	-40	0	n/a
4	-20	0	n/a
5	0	0	n/a

It can be seen that by increasing the initiation temperature of the reaction that no diene **335** is formed, instead returning quantitative amounts of starting material. Conversely, decreasing the reaction temperature provides a significant increase in yield. Although it would be expected that deprotonation of **263** would occur more rapidly at increased temperature, the reaction is not furnishing diene **335** at temperatures above -78 °C. It has been shown that the secondary amine, in this case HMDS, generated *in situ* from the enolisation of carbonyl compounds, has an effect upon the reactivity of the enolate formed.¹⁷⁹ This has been highlighted by the addition of a deuterating reagent to the enolate generated from **345**.¹⁸⁰

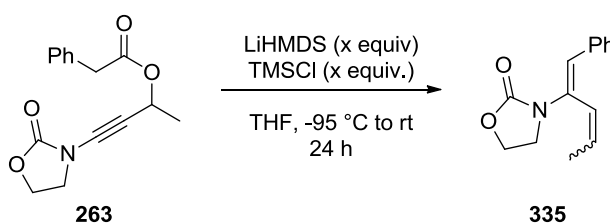


Scheme 106 – Example of internal proton return (IPR)

Instead of the desired α -deutero ester **347**, the major reaction product is the re-protonated ester **345**. It is believed that the secondary amine generated in the reaction is responsible for the returned starting material, by a process termed “Internal Proton Return” (IPR). Work within the Carbery group, focussing on the enamido Ireland-Claisen rearrangement, has also highlighted the importance of IPR within the Ireland-Claisen rearrangement.¹⁸¹ It is believed that the observed return of **263** in our reaction, at temperatures exceeding $-78\text{ }^{\circ}\text{C}$ may be due to HMDS mediated IPR to the enolate, silylketene acetal or both.

As starting material was still being isolated from the ynamido Ireland-Claisen rearrangement it was believed that increasing the equivalents of base used for the initial deprotonation of **263** would increase the yield of the reaction.

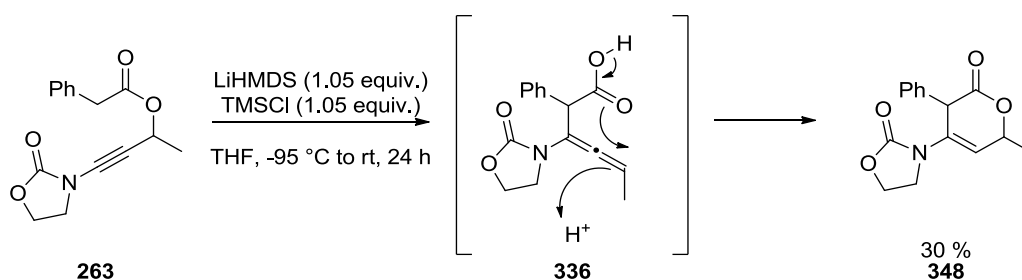
Table 17 – Base screen



Entry	LiHMDS (equiv.)	TMSCl (equiv.)	Yield (%)	Z:E
1	5.2	5.2	0	n/a
2	2.6	2.6	31	1:1
3	2.3	2.3	40	3:1
4	2	2	42	5:1
5	1.8	1.8	83	8:1
6	1.3	1.3	61	>99:1
7	1.05	1.05	19	6:1

It can be observed that when a large excess of base is used no product is obtained, and unlike all the other examples, no starting material can be recovered from this reaction. Lowering the equivalents of base increases the yield of diene **335**, however, now the reaction provides a mixture of Z:E isomers. When 1.8 equivalents of base are used the

maximum yield for the reaction is achieved with good selectivity. As seen previously, the use of 1.3 equivalents of base provides the product as a single isomer in good yield. When near stoichiometric amounts of base are employed, the yield of **335** drops sharply to 19 % as well as the *Z:E* ratio decreasing. Interestingly, an alternative product can also be isolated from this rearrangement.



Scheme 107 – Lactone **348** formation in the ynamido Ireland-Claisen rearrangement of **263**

The lactone **348** formed as part of this reaction has only been isolated when 1.05 equivalents of base has been used for the rearrangement. It is believed that the lactone is formed through intermolecular attack of the carboxylic acid onto allene **336**, mirroring the regioselectivity seen in the gold(I)-catalysed nucleophilic addition of indole to allenamides.

4.5 Ynamido ester scope

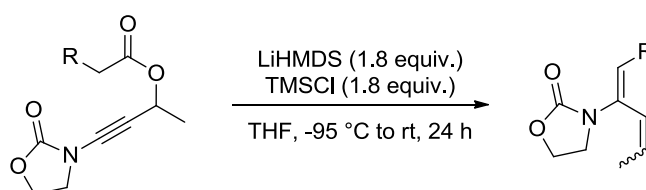
With optimised conditions for the rearrangement of **263**, it was decided to probe the scope of the reaction with regards to the substitution of the ester fragment of the substrate. In order to assess the generality of our ynamido Ireland-Claisen rearrangement, a range of ynamido esters, with varying electronic and steric demands, were first synthesised.

Table 18 – Ynamido ester synthesis

Entry	R	Product	Yield [%]
1	4-ClC ₆ H ₄	349	84
2	4-NO ₂ C ₆ H ₄	350	82
3	3-MeC ₆ H ₄	351	60
4	2-MeC ₆ H ₄	352	58
5	CH ₂ CH ₃	353	83

Halogenated substrate **349** was prepared, along with electron-withdrawing ester **350** to explore the electronic demands of our rearrangement (Table 18, entries 1-2). To assess if alternate substitution patterns would be tolerated in the reaction, tolyl regioisomers **351** and **352** were synthesised (entries 3-4). An alkyl variant **353** was also synthesised to determine if the reaction would tolerate alternate ester functionality (entry 5). Along with ynamido esters synthesised for our gold(I) catalysed rearrangement, these new esters were subjected to our optimised conditions.

Table 19 – Substrate scope for ynamido Ireland-Claisen rearrangement



Entry	Substrate	R	Product	Yield [%]	Z:E
1	289	4-NMe ₂ C ₆ H ₄	354	53	>95:5
2	288	4-OMeC ₆ H ₄	355	62 ^[a]	9:1
3	292	3,4-(O ₂ CH ₂)C ₆ H ₃	356	69	2:1
4	290	4-FC ₆ H ₄	357	67	3:1
5	349	4-ClC ₆ H ₄	358	65	4:1
6	350	4-NO ₂ C ₆ H ₄	359	54	2:1
7	287	4-MeC ₆ H ₄	360	73	3:1
8	351	3-MeC ₆ H ₄	361	42	6:1
9	352	2-MeC ₆ H ₄	362	43	2:1
10	353	CH ₂ CH ₃	363	32 ^[a]	>95:5

[a] 1.3 equivalents of LiHMDS used

Electron rich substrates **289** and **288** rearrange in good yields, providing high levels of *Z:E* selectivity in the diene products **354** and **355** respectively (Table 19, Entries 1 and 2) with methoxyester **288** giving the best results when treated with 1.3 equivalents of base. Piperonylic ester **292** rearrangement proceeded in high yield, however *Z:E* selectivity was lower than that seen for the other electron-donating esters. Halogenated substrates **290** and **349** all rearrange smoothly providing the respective dienes, **357** and **358**, in good yield (entries 3-5). Interestingly, the *Z:E* ratios for these substrates are lower than that for the electron-rich substrates. Electron-poor ester **350** was shown to rearrange well, albeit with poor *Z:E* selectivity. Tolylyl regioisomers all proceeded to give the respective diene products, however *meta*- and *ortho*-products, **361** and **362** respectively, afforded poorer yields than the *para*-tolyl product **360**. Pleasingly, alkyl ester **351** rearranged as a single isomer **363**, however reaction yield is diminished compared to the aromatic analogues.

A possible rationale for the observed reactivity may be due to the stability of the respective enolates formed from both the aromatic and alkyl ynamido esters.

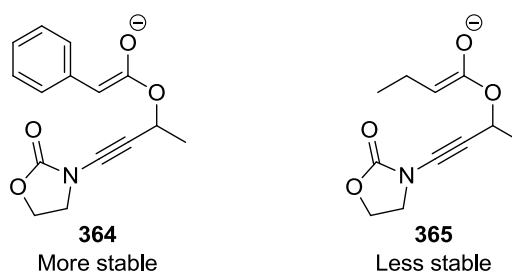


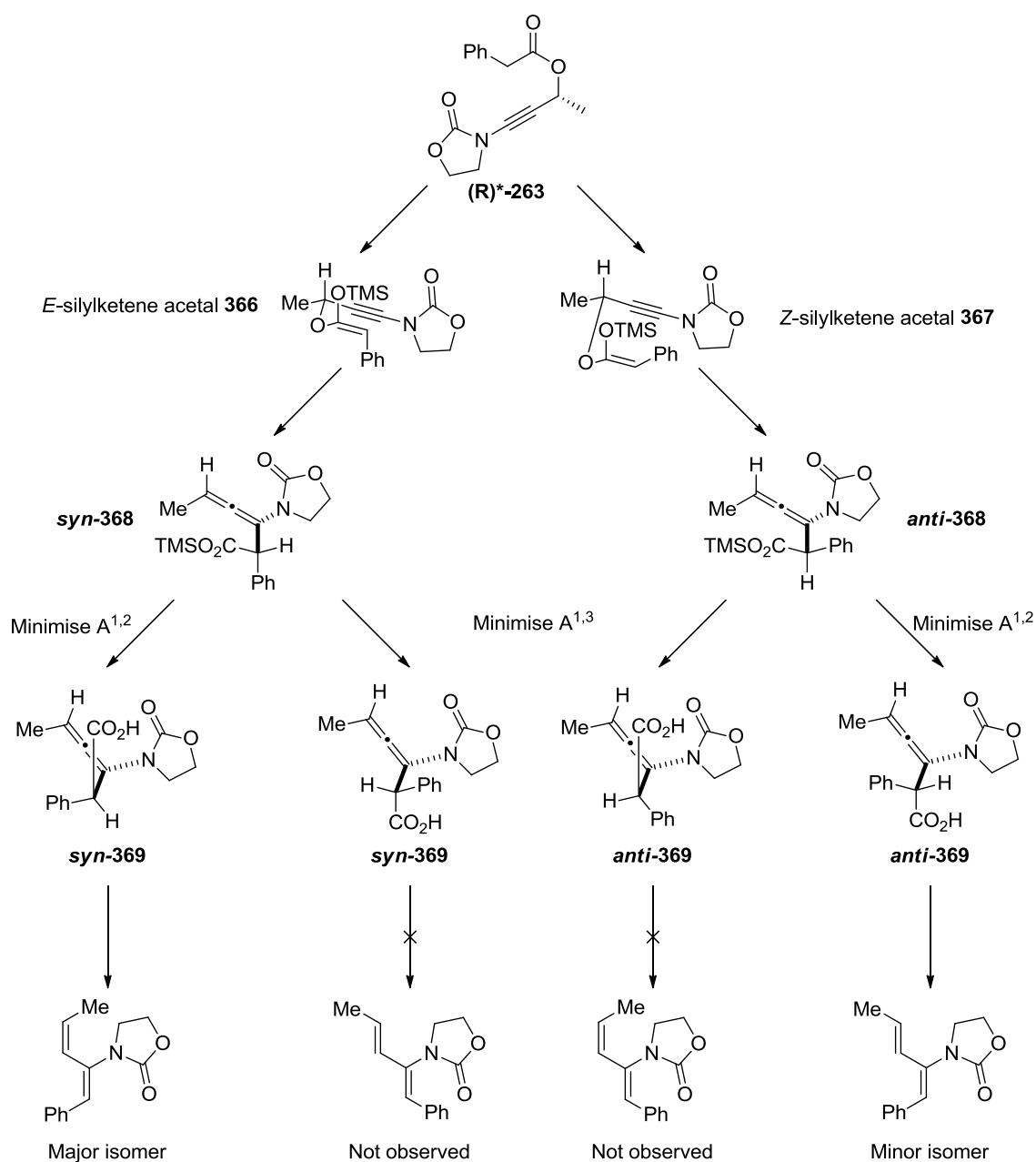
Figure 32 – Enolates generated from **263** and **353** respectively

Enolate **364** may be more stable due to the ability to delocalise the negative charge throughout the aromatic system, which enolate **365** cannot do. The Ireland-Claisen rearrangement requires the silylation of the enolate intermediate, forming a silylketene acetal, to halt the degradation of the intermediate enolate. As enolate **364** is more stable than **365**, it may be longer lived, thus allowing for a higher level of silylketene acetal formation, manifesting in an increased yield of the Ireland-Claisen rearrangement product.

4.5.1 Accounting for observed geometrical isomers

In order to account for the formation of geometrical isomers during the ynamido Ireland-Claisen rearrangement, the following model is proposed. Starting from (**R**)^{*}-**263**, two possible silylketene acetals can be formed, with *E*-silylketene acetal **366** leading to *syn*-**368**, and *Z*-silylketene acetal **367** affording *anti*-**368**. These diastereomers are each capable of adopting two conformations, minimising 1,2- and 1,3-allylic strain respectively. Following decarboxylation, the intermediates generated from minimising 1,3-allylic strain afford the opposite enamide geometry to that observed in our reaction. This indicates that the reduction of 1,2-allylic strain is more important during this transformation. The diastereomers formed from both *E*- and *Z*-silylketene acetals may adopt the conformations seen in scheme 108, resulting from the minimisation of 1,2-allylic strain, which ultimately decarboxylate to afford the major and minor geometrical isomers of **335**. The observed major product from our

rearrangement can be seen to arise from the rearrangement and decarboxylation of the *E*-silylketene acetal **366**.



Scheme 108 – Potential intermediates in the ynamido Ireland-Claisen rearrangement

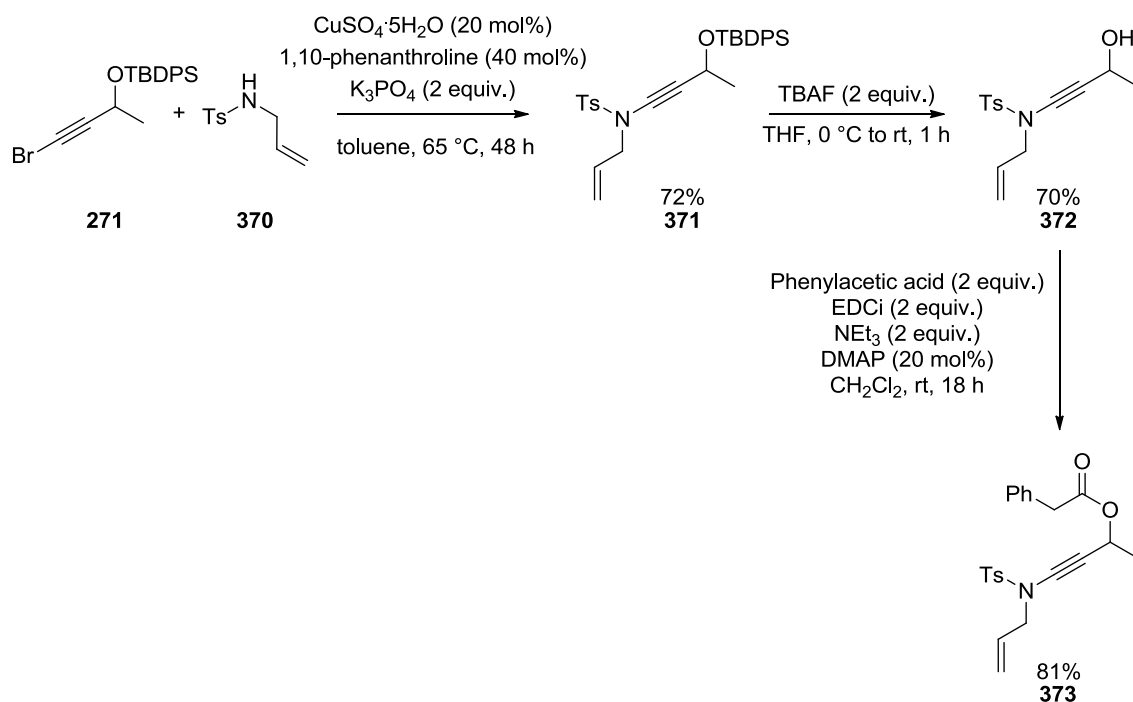
Studies within the Carbery group, following the formation of aryl-substituted silylketene acetals by ^1H NMR, have shown that at low temperatures ($-95\text{ }^\circ\text{C}$), *E*-silylketene acetals are formed exclusively; however at this temperature conversion remains low. Upon warming, there is a significant degradation in the *E/Z* silylketene

acetal ratio, along with a marked increase in the consumption of the starting material.¹⁸² The temperature at which silylation of the enolate formed during the Ireland-Claisen rearrangement is therefore key to the *E/Z* silylketene acetal ratio, and the subsequent geometrical isomer ratio of the diene product **335**. In addition to this, it was found that many other factors also affect the *E/Z* ratio of phenylacetate derived silylketene acetals, including the initiation temperature, nature of the ester alkoxy moiety and the loading of silylating agent.

Although this model accounts for the formation of the major and minor geometrical isomers formed during the ynamido Ireland-Claisen rearrangement, additional studies would be necessary to be able to rationalise the observed *Z/E* ratios of the diene products formed as part of the ynamido Ireland-Claisen rearrangement.

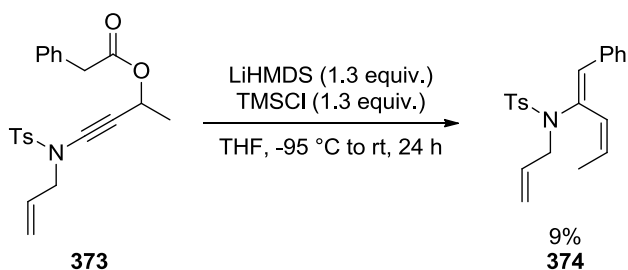
4.6 Alternative *N*-protection in the ynamido Ireland-Claisen rearrangement

With the aim of enhancing the synthetic utility of the ynamido Ireland-Claisen rearrangement, the synthesis of an alternative ynamido ester was investigated to probe the effect on reactivity of modulating the electronic donating ability of the ynamide nitrogen. To allow for the cleavage of the ynamide fragment post rearrangement, *p*-tolylsulfonamide was selected (cleaved by Mg/MeOH).¹⁸³ The other *N*-substituent could be fulfilled by an allyl group (cleaved by Wilkinson's catalyst), allowing for orthogonal protection of the ynamide nitrogen.¹⁸⁴



Scheme 109 – Synthesis of sulfonamide 373

Utilising the procedure for the synthesis of our model ynamide substrate **263**, sulfonamide **371** was prepared from bromoalkyne **271**. The initial Ullman coupling proceeded in good yield, with subsequent deprotection and carbodiimide promoted esterification affording sulfonamide **373** in good yield. Having synthesised the required substrate, it was subjected to our optimised reaction conditions.



Scheme 110 – Ireland-Claisen rearrangement of sulfonamide 373

Although **373** rearranges with associated decarboxylation, the yield for this reaction is poor compared to those of oxazolidinone ynamides. A possible rational for such disparities in reactivity between the allylsulfonamide and oxazolidinone containing substrates could be attributed to the pKa of the respective parent amines. As previously discussed in the hypothesised mechanism of this reaction; the ability for the nitrogen

lone-pair to be donated into the alkyne is key for the decarboxylation to occur. Allylsulfonamide **370** has a lower pKa (~16.1 in DMSO) than oxazolidinone **272** (~20.8 in DMSO),¹⁸⁵ implying that the nitrogen lone pair in the sulfonamide is less available, and therefore less able to be donated into the alkyne system.

4.7 Diels-Alder reaction of Ireland-Claisen product **335**

To establish the synthetic utility of the products formed as part of this work, a Diels-Alder reaction was attempted on the diene formed from the Ireland-Claisen rearrangement. Following the procedure developed by Hsung *et al.* for the Diels-Alder reaction of amino dienes, **335** and maleic anhydride **375** were stirred together in toluene at reflux.¹⁸⁶



Scheme 111 – Attempted Diels-Alder reaction of **335**

Unfortunately, the cycloaddition failed to occur, with quantitative starting material being isolated from this reaction. In order for this Diels-Alder reaction to proceed, the diene **335** must adopt the *cis*-conformation to allow for required interaction with the LUMO of **375**, however due to steric interactions, it is believed that **335** adopts the *trans*-conformation.

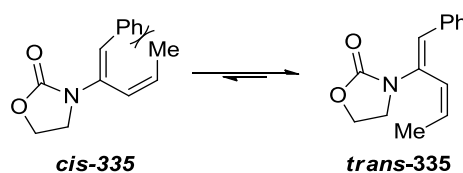


Figure 33 – Potential orientation of **335**

4.8 Conclusions

A novel ynamido variant of the Ireland-Claisen rearrangement has been reported, the products of which undergo facile decarboxylation at ambient temperature, which is unprecedented for systems of this type.

An extensive programme of optimisation has been undertaken to increase the synthetic utility of this reaction, with good yield and high *Z:E* selectivities possible for ynamido ester **263**.

A range of electronically differentiated arylacetate ynamido esters have been synthesised and rearranged, showing our reaction protocol to be general with respect to the ester fragment of our ynamides. Attempts to alter the ynamide moiety have proved unsuccessful, with sulfonamide **373** rearranging in poor yield.

Attempted Diels Alder cyclisation of our amino diene products has proved unsuccessful, potentially due to the *E/Z* conformation of the diene formed in our reaction.

4.9 Future work

Although the ester fragment of our substrate has been explored, the ynamide fragment has received limited attention. To address this, a range of ynamides could be synthesised from carbamate **377**, acetamide **378** and imidazolidin-2-one **379** could be utilised.

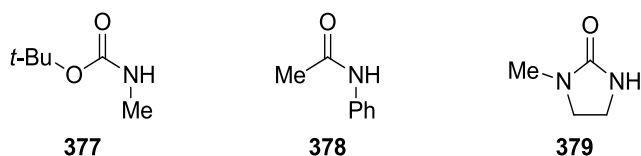


Figure 34 – Carbamate **377**, acetamide **378** and imidazolidin-2-one **379**

Although a tentative mechanism has been provided for the ynamido Ireland-Claisen rearrangement, it may be possible to carry out *in situ* ^{13}C NMR monitoring of the reaction to determine precisely when decarboxylation occurs. This would require the synthesis of a ^{13}C enriched substrate to be synthesised.

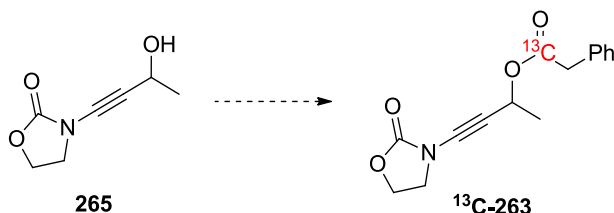


Figure 35 – Carbon labelled substrate for ^{13}C NMR studies

A possible method for confirming the presence of alleneamide **336** would involve trapping the intermediate with a suitable electrophile, potentially inhibiting decarboxylation in our reaction.

5. EXPERIMENTAL

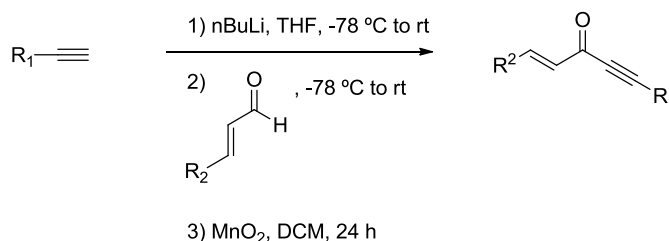
5.1 General Information

All reactions were carried out using anhydrous solvents and under an inert atmosphere of nitrogen. All reaction vessels were flame dried before use. Solvents were obtained by passing through anhydrous alumina columns using an Innovative Technology Inc. PS-400-7 solvent purification system. All reagents were purchased from commercial suppliers: Acros Organics, Alfa Aesar, Sigma Aldrich or Novabiochem and used without further purification. Triethylamine was freshly distilled prior to use and chlorotrimethylsilane was freshly distilled from 10 % quinoline. All distilled materials were stored under nitrogen in a fridge. All reactions were monitored by thin layer chromatography (TLC) using pre-coated MN Alugram Sil G/UV254 silica gel 60 aluminium backed plates. Plates were developed using standard techniques, UV light followed by a chemical dip, usually KMnO_4 and gentle heating. Flash chromatography was performed on chromatography grade, silica 60Å particle size 35-70 micron from Fisher Scientific using the solvent system as stated.

^1H and ^{13}C NMR was performed on Brüker Avance 250 (^1H 250 MHz), Brüker Avance 300 (^1H 300 MHz and ^{13}C 75 MHz), Brüker Avance 400 (^1H 400 MHz and ^{13}C 100 MHz) and Brüker Avance 500 (^1H 500 MHz and ^{13}C 125 MHz) as stated. Chemical shifts are reported in parts per million (ppm) relative to tetramethylsilane (TMS) ($\delta = 0.00$). Coupling constants are reported in Hertz (Hz) and signal multiplicity is denoted as singlet (s), doublet (d), triplet (t), quartet (q), septet (sept), multiplet (m), and broad (br. s). Mass spectroscopy was performed on a Brüker μTOF using electrospray ionisation (ESI) in either positive or negative ionisation as stated. Infra-red spectroscopy was carried out using a Perkin Elmer Spectrum RX FT-IR system with KBr plates, using a thin film. Melting points were determined using a Bibby Scientific Melting point apparatus Stuart SMP10 digital. X-ray data was collected at 150 K on a Nonius KappaCCD area diffractometer using Mo-K α radiation ($\lambda = 0.71073 \text{ \AA}$) and all structures were solved by direct methods and refined on all F 2 data using SHELXL-97 suite of programs. Hydrogen atoms included in idealised positions and refined using the riding model.

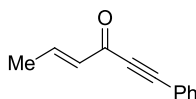
5.2 Chapter 2

5.2.1 General Procedure A for synthesis of enynone¹⁸⁷



To a stirred solution of alkyne (1 equiv.) in THF (15 mL/mmol) at -78°C , was added $n\text{BuLi}$ (1.6 M in hex., 1.1 equiv.) dropwise and stirred for 10 minutes. The solution was warmed to room temperature, then stirred for 20 minutes before returning to -78°C . A solution of aldehyde (1 equiv.) in THF (5 mL) was added and the reaction warmed to room temperature and stirred for 4 hours. NH_4Cl (sat.) (100 mL) was added and the product was extracted with EtOAc (3×100 mL), washed with brine (100 mL), dried over Na_2SO_4 , filtered and concentrated *in vacuo* to afford a crude residue. The crude residue was then dissolved in DCM (15 mL/mmol), and treated with manganese dioxide (25 equiv.) and stirred for 24 hours. The mixture was filtered through celite then concentrated *in vacuo*. Purification was achieved by flash chromatography, eluting with 8:1 Pet/EtOAc, to afford the enynone.

(*E*)-1-Phenylhex-4-en-1-yn-3-one (147)

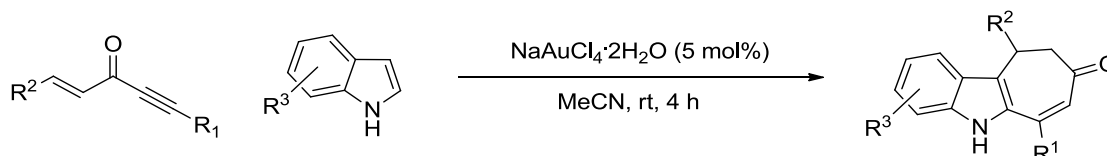


Prepared according to general procedure A, using phenyl acetylene (1.07 mL, 9.79 mmol, 1 equiv.), crotonaldehyde (800 μL , 9.79 mmol, 1 equiv.), $n\text{BuLi}$ (1.6M in Hex., 6.70 mL, 10.7 mmol, 1.1 equiv.), THF (150 mL), manganese dioxide (19.3 g, 222 mmol, 25 equiv.), DCM (150 mL). Purification was achieved by flash chromatography to afford **147** as a pale yellow oil (0.94 g, 64%).

^1H NMR (CDCl_3 , 500 MHz) δ_{H} : 7.27–7.62 (6H, m), 6.28 (1H, dq, $J = 15.6, 1.7$ Hz), 2.04 (3H, dd, $J = 6.9, 1.7$ Hz); ^{13}C NMR (CDCl_3 , 125 MHz) δ_{C} : 178.4, 149.5, 134.0, 132.9, 130.5, 128.6, 120.2, 91.1, 86.2, 18.5.

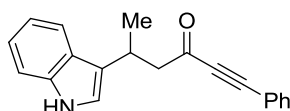
All data is in accordance to reported literature values¹⁸⁸

5.2.2 General procedure B for double hydroarylation of indole with enynones



To indole (1.05 equiv.) in a round bottomed flask was added a solution of enynone (1 equiv.) in acetonitrile (1 mL) followed by a solution of sodium tetrachloroaurate (III) hydrate (5 mol%) in acetonitrile (1 mL) and stirred at room temperature for 4 hours. The solution was filtered through celite and concentrated in vacuo. Subsequent purification by flash chromatography eluting with 8:1 Pet/EtOAc afforded tricycle.

5-(1H-Indol-3-yl)-1-phenylhex-1-yn-3-one (150)

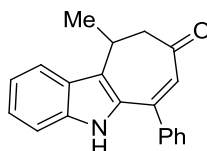


To a solution of **147** (280 mg, 1.90 mmol, 1 equiv.) in acetonitrile (10 mL) at 0 °C was added DNsOH (23 mg, 0.10 mmol, 5 mol%) portionwise, then the reaction was allowed to stir for 40 minutes. Upon completion, the reaction was filtered through K_2CO_3 and concentrated *in vacuo*. Purification was achieved by flash chromatography to provide the title compound as a yellow oil (404 mg, 81%).

FTIR (thin film) ν_{max} : 3414, 3057, 2963, 2928, 2199, 1654; ^1H NMR (500 MHz, CDCl_3) δ_{H} : 7.95 (1H, br. s), 7.64 (1H, d, $J = 7.5$ Hz), 7.46–7.31 (3H, m), 7.30–7.19 (3H, m), 7.18–7.02 (2H, m), 6.91 (1H, d, $J = 2.4$ Hz), 3.84–3.69 (1H, m), 3.12 (1H, dd, $J = 15.5, 6.0$ Hz), 2.86 (1H, dd, $J = 15.5, 8.4$ Hz), 1.40 (3H, d, $J = 7.2$ Hz); ^{13}C NMR (125 MHz, CDCl_3) δ_{C} : 187.7, 136.6, 133.1, 130.7, 128.6, 126.4, 122.1, 120.5, 120.4, 120.0,

119.4, 119.1, 111.5, 91.2, 88.1, 53.2, 27.7, 21.1; HRMS (ESI, +ve) m/z : calcd. for $C_{20}H_{17}NONa$: 310.1208, found: 310.1219 $[M + H]^+$.

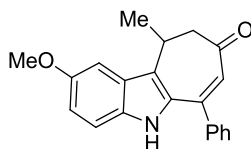
10-Methyl-6-phenyl-9,10-dihydrocyclohepta[b]indol-8(5H)-one (148)



Prepared according to general procedure B (reaction time = 4 h), using indole (25 mg, 0.21 mmol, 1.05 equiv.), diphenylpent-1-en-4-yn-3-one (34 mg, 0.2 mmol, 1 equiv.), sodium tetrachloroaurate (III) hydrate (4 mg, 0.01 mmol, 5 mol%), acetonitrile (2 mL). Purification was achieved by flash chromatography (8:1 Pet/EtOAc) afforded a yellow solid. Recrystallisation from petrol/DCM afforded **148** as a yellow solid (57 mg, 100%).

MP: 170 – 171 °C. FTIR (thin film) ν_{\max} : 3057, 2956, 2924, 1707, 1623; 1H NMR (500 MHz, $CDCl_3$) δ_H : 7.73 (1H, br. s), 7.70-7.17 (8H, m), 6.20 (1H, s), 3.61–3.38 (1H, m), 3.19 (1H, dd, J = 14.4, 3.1 Hz), 2.97 (1H, dd, J = 14.4, 1.8 Hz), 1.37 (3H, d, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C : 199.9, 145.2, 139.7, 135.5, 129.9, 129.3, 129.0, 128.9, 128.5, 126.8, 126.2, 124.7, 120.4, 119.5, 111.4, 48.2, 25.0, 17.1; HRMS (ESI, +ve) m/z : calcd. for $C_{20}H_{17}ONNa$: 310.1208, found 310.1606 $[M + Na]^+$.

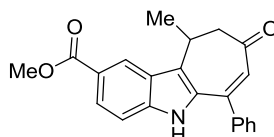
2-Methoxy-10-methyl-6-phenyl-9,10-dihydrocyclohepta[b]indol-8(5H)-one (157)



Prepared according to general procedure B (reaction time = 4 h), using 5-methoxyindole (31 mg, 0.21 mmol, 1.05 equiv.), **147** (34 mg, 0.20 mmol, 1 equiv.), sodium tetrachloroaurate (III) hydrate (4 mg 0.01 mmol, 5 mol%), acetonitrile (2 mL). Purification was achieved by flash chromatography to afford **157** as a yellow oil (57 mg, 90%).

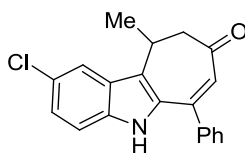
FTIR (thin film) ν_{max} : 2959, 2831, 1718, 1623, 1582, 1567, 1533; ^1H NMR (500 MHz, CDCl_3) δ_{H} : 7.63 (1H, br. s), 7.52–7.44 (5H, m), 7.20–7.16 (2H, m), 7.04 (1H, d, $J = 2.3$ Hz), 6.94 (1H, dd, $J = 8.8, 2.3$ Hz), 6.17 (1H, d, $J = 1.6$ Hz), 3.90 (s, 3H), 3.61–3.55 (1H, m), 3.20 (1H, dd, $J = 14.7, 3.5$ Hz), 2.96 (1H, dd, $J = 14.7, 5.6$ Hz), 1.36 (3H, d, $J = 7.5$ Hz); ^{13}C NMR (75 MHz, CDCl_3) δ_{C} : 199.8, 154.6, 130.9, 129.2, 128.9, 128.5, 128.2, 125.7, 122.3, 116.0, 99.8, 55.8, 48.2, 25.0, 17.0; HRMS (ESI, +ve) m/z : calcd. for $\text{C}_{21}\text{H}_{19}\text{NO}_2\text{Na}$ 340.1313, found 340.1303 $[\text{M} + \text{Na}]^+$.

Methyl 10-methyl-8-oxo-6-phenyl-5,8,9,10-tetrahydrocyclohepta[b]indole-2-carboxylate (158)



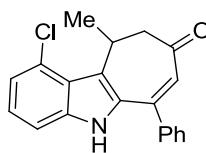
Prepared according to general procedure B (reaction time = 24 h), using methyl indole-5-carboxylate (37 mg, 0.21 mmol, 1.05 equiv.), **147** (34 mg, 0.20 mmol, 1 equiv.), sodium tetrachloroaurate (III) hydrate (4 mg 0.01 mmol, 5 mol%), acetonitrile (2 mL). Purification was achieved by flash chromatography to afford **158** as a yellow oil (49 mg, 71%).

FTIR (thin film) ν_{max} : 2956, 2897, 1711, 1625, 1541, 1512; ^1H NMR (500 MHz, CDCl_3) δ_{H} : 8.46 (1H, br. s), 7.96–7.94 (2H, m), 7.53–7.44 (5H, m), 7.29–7.25 (2H, m), 7.20–7.16 (1H, m), 6.24 (1H, d, $J = 1.6$ Hz), 3.97 (3H, s), 3.74–3.66 (1H, m), 3.18 (1H, dd, $J = 14.7, 3.3$ Hz), 2.98 (1H, dd, $J = 14.7, 5.1$ Hz), 1.38 (3H, d, $J = 7.5$ Hz); ^{13}C NMR (75 MHz, CDCl_3) δ_{C} : 199.5, 167.7, 144.4, 139.3, 131.2, 129.7, 129.4, 129.0, 128.5, 128.2, 127.2, 126.5, 125.6, 122.6, 122.5, 111.1, 52.0, 48.0, 24.9, 17.1; HRMS (ESI, +ve) m/z : calcd. for $\text{C}_{22}\text{H}_{20}\text{NO}_3$ 346.1443, found 346.1441 $[\text{M} + \text{H}]^+$.

2-Chloro-10-methyl-6-phenyl-9,10-dihydrocyclohepta[b]indol-8(5H)-one (159)

Prepared according to general procedure B (reaction time = 4 h), using To 5-chloroindole (32 mg, 0.21 mmol, 1.05 equiv.), **147** (34 mg, 0.20 mmol, 1 equiv.), sodium tetrachloroaurate (III) hydrate (4 mg, 0.01 mmol, 5 mol%), acetonitrile (2 mL). Purification was achieved by flash chromatography to afford **159** as a yellow oil (62 mg, 96%).

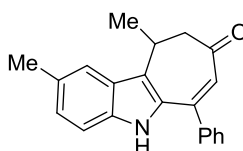
FTIR (thin film) ν_{\max} : 2963, 2925, 2849, 1734, 1630, 1535; ^1H NMR (500 MHz, CDCl_3) δ_{H} : 7.77 (1H, br. s), 7.65–7.63 (1H, m), 7.54–7.51 (3H, m), 7.48–7.44 (2H, m), 7.20–7.19 (2H, m), 6.23 (1H, d, $J = 1.6$ Hz), 3.59–3.53 (1H, m), 3.16 (1H, dd, $J = 14.6, 3.2$ Hz), 2.96 (1H, dd, $J = 14.6, 5.3$ Hz), 1.35 (3H, d, $J = 7.3$ Hz); ^{13}C NMR (75 MHz, CDCl_3) δ_{C} : 199.5, 144.5, 139.4, 133.7, 131.1, 129.5, 129.4, 129.1, 128.5, 127.8, 126.1, 125.3, 125.0, 118.8, 112.5, 48.1, 25.0, 17.1; HRMS (ESI, +ve) m/z : calcd. for $\text{C}_{20}\text{H}_{17}\text{ClNO}$ 322.0999, found 322.0978 $[\text{M} + \text{H}]^+$.

1-Chloro-10-methyl-6-phenyl-9,10-dihydrocyclohepta[b]indol-8(5H)-one (160)

Prepared according to general procedure B (reaction time = 4 h), using 4-chloro indole (32 mg, 0.21 mmol, 1.05 equiv.), **147** (34 mg, 0.20 mmol, 1 equiv.), sodium tetrachloroaurate (III) hydrate (4 mg 0.01 mmol, 5 mol%), acetonitrile (2 mL). Purification was achieved by flash chromatography to afford **160** as a yellow oil (51 mg, 80%).

FTIR (thin film) ν_{\max} : 3060, 3028, 2922, 2865, 1734, 1651, 1537; ^1H NMR (500 MHz, CDCl_3) δ_{H} : 7.82 (1H, br. s), 7.51–7.35 (3H, m), 7.45–7.42 (2H, m), 7.16–7.12 (3H, m), 6.23 (1H, d, $J = 2.0$ Hz), 4.53–4.47 (1H, m), 3.20 (1H, dd, $J = 14.7, 3.0$ Hz), 2.95 (1H, dd, $J = 14.7, 2.0$ Hz), 1.38 (3H, d, $J = 7.4$ Hz); ^{13}C NMR (75 MHz, CDCl_3) δ_{C} : 199.9, 150.1, 144.7, 139.7, 136.7, 131.0, 129.8, 129.3, 129.1, 128.5, 127.2, 126.5, 124.8, 121.9, 110.1, 47.9, 24.7, 17.1; HRMS (ESI, +ve) m/z : calcd. for $\text{C}_{20}\text{H}_{16}\text{ClNO}$ 322.0999, found 322.0980 $[\text{M} + \text{H}]^+$.

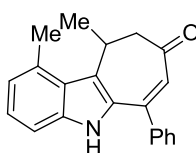
2,10-Dimethyl-6-phenyl-9,10-dihydrocyclohepta[b]indol-8(5H)-one (161)



Prepared according to general procedure B (reaction time = 4 h), using 5-methylindole (28 mg, 0.21 mmol, 1.05 equiv.), **147** (34 mg, 0.20 mmol, 1 equiv.), sodium tetrachloroaurate (III) hydrate (4 mg, 0.01 mmol, 5 mol%), acetonitrile (2 mL). Purification was achieved by flash chromatography to afford **161** as a yellow oil (58 mg, 96%).

FTIR (thin film) ν_{\max} : 2970, 2933, 2884, 1768, 1659; ^1H NMR (500 MHz, CDCl_3) δ_{H} : 7.64 (1H, br. s), 7.52–7.45 (6H, m), 7.16 (1H, d, $J = 8.5$ Hz), 7.09 (1H, dd, $J = 8.5, 1.3$ Hz), 6.17 (1H, d, $J = 1.6$ Hz), 3.64–3.58 (1H, m), 3.18 (1H, dd, $J = 14.4, 3.3$ Hz), 2.95 (1H, dd, $J = 14.4, 5.4$ Hz), 2.48 (3H, s), 1.35 (3H, d, $J = 7.2$ Hz); ^{13}C NMR (75 MHz, CDCl_3) δ : 199.9, 145.3, 129.8, 129.2, 128.9, 128.5, 126.6, 125.7, 118.8, 111.1, 48.2, 29.7, 24.9, 21.6, 17.0; HRMS (ESI, +ve) m/z : calcd. for $\text{C}_{21}\text{H}_{20}\text{NO}$ 302.1545, found 302.1539 $[\text{M} + \text{H}]^+$.

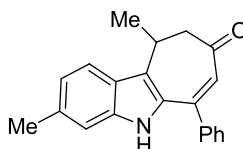
1,10-Dimethyl-6-phenyl-9,10-dihydrocyclohepta[b]indol-8(5H)-one (162)



Prepared according to general procedure B (reaction time = 4 h), using 4-methylindole (27.5 mg, 0.21 mmol, 1.05 equiv.), **147** (34 mg, 0.20 mmol, 1 equiv.), sodium tetrachloroaurate (III) hydrate (4 mg, 0.01 mmol, 5 mol%), acetonitrile (2 mL). Purification was achieved by flash chromatography to afford **162** as a yellow oil (56 mg, 93%).

FTIR (thin film) ν_{max} : 3056, 2965, 2864, 1729, 1625, 1570, 1523; ^1H NMR (500 MHz, CDCl_3) δ_{H} : 7.72 (1H, br. s), 7.52–7.43 (5H, m), 7.14–7.07 (2H, m), 6.89 (1H, dt, $J = 6.7, 1.2$ Hz), 6.19 (1H, d, $J = 1.8$ Hz), 4.06–4.00 (1H, m), 3.23 (1H, dd, $J = 14.8, 3.2$ Hz), 2.95 (1H, dd, $J = 14.8, 5.5$ Hz), 2.79 (3H, s), 1.38 (3H, d, $J = 7.4$ Hz); ^{13}C NMR (75 MHz, CDCl_3) δ_{C} : 199.8, 145.6, 140.1, 135.8, 135.8, 131.8, 129.9, 129.2, 128.9, 128.6, 127.8, 124.7, 122.5, 109.4, 48.2, 25.7, 20.9, 17.1; HRMS (ESI, +ve) m/z : calcd. for $\text{C}_{21}\text{H}_{20}\text{NO}$ 302.1545, found 302.1542 $[\text{M} + \text{H}]^+$.

3,10-Dimethyl-6-phenyl-9,10-dihydrocyclohepta[b]indol-8(5H)-one (**163**)

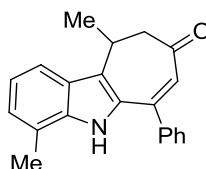


Prepared according to general procedure B (reaction time = 4 h), using 6-methylindole (28 mg, 0.21 mmol, 1.05 equiv.), **147** (34 mg, 0.20 mmol, 1 equiv.), sodium tetrachloroaurate (III) hydrate (4 mg, 0.01 mmol, 5 mol%), acetonitrile (2 mL). Purification was achieved by flash chromatography to afford **163** as a yellow oil (57 mg, 96%).

FTIR (thin film) ν_{max} : 3054, 2965, 2867, 1735, 1625, 1570, 1523. ^1H NMR (500 MHz, CDCl_3) δ_{H} : 7.70 (1H, br. s), 7.56 (1H, d, $J = 8.0$ Hz), 7.52–7.44 (5H, m), 7.07–7.06 (1H, m), 7.02 (1H, dd, $J = 8.0, 1.2$ Hz), 6.16 (1H, d, $J = 1.6$ Hz), 3.63–3.57 (1H, m), 3.18 (1H, dd, $J = 14.7, 3.9$ Hz), 2.94 (1H, dd, $J = 14.7, 5.4$ Hz), 2.46 (3H, s), 1.35 (3H, d, $J = 7.4$ Hz); ^{13}C NMR (75 MHz, CDCl_3) δ_{C} : 199.9, 145.4, 139.9, 136.1, 135.0, 129.4,

129.2, 128.9, 128.5, 128.3, 126.4, 124.7, 122.4, 119.1, 111.1, 48.2, 25.0, 17.0; HRMS (ESI, +ve) m/z : calcd. for $C_{21}H_{20}NO$ 302.1540, found 302.1539 $[M + H]^+$.

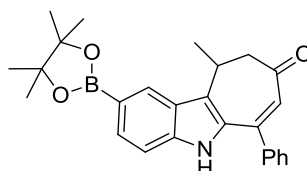
4,10-Dimethyl-6-phenyl-9,10-dihydrocyclohepta[b]indol-8(5H)-one (164)



Prepared according to general procedure B (reaction time = 4 h), using 7-methylindole (28 mg, 0.21 mmol, 1.05 equiv.), **147** (34 mg, 0.20 mmol, 1 equiv.), sodium tetrachloraurate (III) hydrate (4 mg, 0.01 mmol, 5 mol%), acetonitrile (2 mL). Purification was achieved by flash chromatography to afford **164** as a yellow oil (56 mg, 95%).

FTIR (thin film) ν_{\max} : 2965, 2928, 2864, 1732, 1626, 1571, 1524; 1H NMR (500 MHz, $CDCl_3$) δ_H : 7.75 (1H, br. s), 7.52–7.42 (5H, m), 7.14–7.08 (2H, m), 6.89 (1H, dt, $J = 6.9, 1.0$ Hz), 6.19 (1H, d, $J = 1.9$ Hz), 4.06–4.00 (1H, m), 3.23 (1H, dd, $J = 14.7, 3.0$ Hz), 2.95 (1H, dd, $J = 14.7, 5.7$), 2.79 (3H, s), 1.39 (3H, d, $J = 7.2$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C : 199.8, 144.7, 140.1, 135.8, 131.8, 129.9, 129.2, 128.9, 128.6, 128.5, 127.8, 125.3, 124.7, 122.5, 109.4, 48.2, 25.7, 20.9, 17.1; HRMS (ESI, +ve) m/z : calcd. for $C_{21}H_{20}NO$ 302.1554, found 302.1539 $[M + H]^+$.

10-Methyl-6-phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-9,10-dihydrocyclohepta[b]indol-8(5H)-one (165)

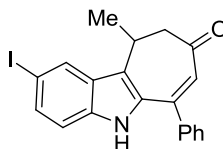


Prepared according to general procedure B (reaction time = 4 h), using 5-indoleboronic acid pinacol ester (51 mg, 0.21 mmol, 1.05 equiv.), **147** (34 mg, 0.20 mmol, 1 equiv.),

sodium tetrachloroaurate (III) hydrate (4 mg 0.01 mmol, 5 mol%), acetonitrile (2 mL). Purification was achieved by flash chromatography to afford **165** as an amorphous yellow solid (73 mg, 88%).

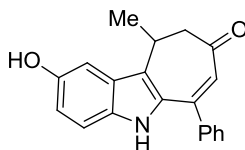
FTIR (thin film) ν_{\max} : 2976, 2931, 1718, 1626, 1541, 1512; ^1H NMR (500 MHz, CDCl_3) δ_{H} : 8.12 (1H, s), 7.72 (1H, br. s), 7.61 (1H, dd, $J = 8.3, 0.9$ Hz), 7.44–7.35 (5H, m), 7.16 (1H, dd, $J = 8.3, 0.9$ Hz), 6.10 (1H, d, $J = 1.5$ Hz), 3.68–3.58 (1H, m), 3.06 (1H, dd, $J = 14.7, 3.4$ Hz), 2.85 (1H, dd, $J = 14.7, 1.5$ Hz), 1.31–1.25 (15H, m); ^{13}C NMR (75 MHz, CDCl_3) δ_{C} : 199.8, 145.0, 139.6, 137.4, 130.6, 129.9, 129.3, 129.0, 128.5, 127.4, 126.9, 126.5, 110.7, 83.7, 48.1, 25.0, 24.9, 24.7, 16.9; HRMS (ESI, +ve) m/z : calcd. for $\text{C}_{26}\text{H}_{29}\text{BNO}_3$ 414.2240, found 414.2255 $[\text{M} + \text{Na}]^+$.

2-Iodo-10-methyl-6-phenyl-9,10-dihydrocyclohepta[b]indol-8(5H)-one (**166**)



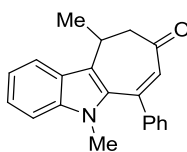
Prepared according to general procedure B (reaction time = 4 h), using 5-iodoindole (51 mg, 0.21 mmol, 1.05 equiv.), **147** (34 mg, 0.20 mmol, 1 equiv.), sodium tetrachloroaurate (III) hydrate (4 mg 0.01 mmol, 5 mol%), acetonitrile (2 mL). Purification by flash chromatography afforded **166** as an amorphous yellow solid (81 mg, 98%).

FTIR (thin film) ν_{\max} : 2960, 2928, 1720, 1626, 1582, 1535; ^1H NMR (500 MHz, CDCl_3) δ_{H} : 8.02 (1H, d, $J = 8.5$ Hz), 7.78 (1H, br. s), 7.54–7.43 (6H, m), 7.05 (1H, d, $J = 8.5$ Hz), 6.22 (1H, d, $J = 1.8$ Hz), 3.58–3.52 (1H, m), 3.15 (1H, dd, $J = 14.9, 3.2$ Hz), 2.95 (1H, dd, $J = 14.9, 5.4$ Hz), 1.34 (3H, d, $J = 7.5$ Hz); ^{13}C NMR (75 MHz, CDCl_3) δ_{C} : 199.5, 144.5, 139.3, 134.3, 132.8, 130.5, 129.6, 129.4, 129.3, 129.1, 128.5, 128.4, 124.9, 113.3, 83.7, 48.0, 24.9, 17.1; HRMS (ESI, +ve) m/z : calcd. for $\text{C}_{20}\text{H}_{16}\text{INONa}$ 436.0174, found 436.0167 $[\text{M} + \text{Na}]^+$.

2-Hydroxy-10-methyl-6-phenyl-9,10-dihydrocyclohepta[b]indol-8(5H)-one (167)

Prepared according to general procedure B (reaction time = 4 h), using 5-hydroxy indole (28 mg, 0.21 mmol, 1.05 equiv.), **147** (34 mg, 0.2 mmol, 1 equiv.), sodium tetrachloroaurate (III) hydrate (4 mg 0.01 mmol, 5 mol%), acetonitrile (2 mL). Purification was achieved by flash chromatography to afford **167** as a yellow solid (55 mg, 92%).

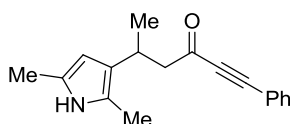
MP: 111 – 114 °C; FTIR (thin film) ν_{max} : 3314, 2959, 1712, 1611, 1581; ^1H NMR (500 MHz, CDCl_3) δ_{H} : 7.62 (1H, br. s), 7.52–7.45 (5H, m), 7.14 (1H, d, J = 8.7 Hz), 7.05 (1H, d, J = 2.3 Hz), 6.86 (1H, dd, J = 8.7, 2.3 Hz), 6.18 (1H, d, J = 1.6 Hz), 4.92 (1H, br. s), 3.53–3.48 (1H, m), 3.18 (1H, d, J = 14.9, 3.4 Hz), 2.95 (1H, dd, J = 14.9, 5.4 Hz), 1.33 (3H, d, J = 7.4 Hz); ^{13}C NMR (75 MHz, CDCl_3) δ_{C} : 200.0, 150.0, 145.2, 139.7, 131.0, 130.9, 129.2, 128.9, 128.7, 128.5, 127.4, 125.3, 115.3, 112.3, 103.0, 48.2, 25.1, 17.0; HRMS (ESI, +ve) m/z : calcd. for $\text{C}_{20}\text{H}_{18}\text{NO}_2$ 304.1338, found 304.1297 [$\text{M} + \text{H}$] $^+$.

5,10-Dimethyl-6-phenyl-9,10-dihydrocyclohepta[b]indol-8(5H)-one (169)

Prepared according to general procedure B (reaction time = 4 h, RT), using 1-methyl-1H-indole (41 μL , 0.32 mmol, 1.05 equiv.), **147** (50 mg, 0.29 mmol, 1 equiv.), sodium tetrachloroaurate (III) hydrate (6 mg, 0.015 mmol, 5 mol%), acetonitrile (2 mL). Purification by flash chromatography afforded **169** as a yellow oil (63 mg, 71%).

FTIR (thin film) ν_{\max} : 2981, 2888, 1638, 1566, 1531; ^1H NMR (500 MHz, CDCl_3) δ_{H} : 7.80 (1H, app.d., $J = 8.0$ Hz), 7.55–7.44 (3H, m), 7.44–7.37 (2H, m), 7.35 (1H, app.d., $J = 7.5$ Hz), 7.33–7.28 (1H, m), 7.24 (1H, app.t., $J = 7.5$ Hz), 6.47 (1H, s), 3.74–3.61 (1H, m), 3.13 (3H, s), 3.09 (1H, app.d., $J = 17.5$ Hz), 3.00 (1H, dd, $J = 17.5, 6.1$ Hz), 1.59 (3H, d, $J = 7.2$ Hz); ^{13}C NMR (125 MHz, CDCl_3) δ_{C} : 201.2, 144.9, 141.6, 138.9, 133.5, 130.8, 129.0, 128.8, 127.6, 125.9, 125.2, 123.9, 119.9, 119.6, 109.9, 52.4, 32.9, 25.4, 15.6; HRMS (ESI, +ve) m/z : calcd. for $\text{C}_{21}\text{H}_{20}\text{NO}$: 302.1545, found: 302.1551 [$\text{M} + \text{H}$] $^+$.

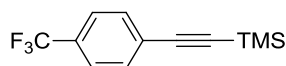
5-(2,5-Dimethyl-1H-pyrrol-3-yl)-1-phenylhex-1-yn-3-one (173)



Prepared according to general procedure B (reaction time = 16 h, reflux), using 2,5-dimethylpyrrole (31 μL , 0.31 mmol, 1.05 equiv.), **147** (50 mg, 0.29 mmol, 1 equiv.), sodium tetrachloroaurate (III) hydrate (6 mg, 0.015 mmol, 5 mol%), acetonitrile (2 mL). Purification by flash chromatography afforded **173** as a yellow oil (38 mg, 49%, 69% BRSM).

FTIR (thin film) ν_{\max} : 3655, 3365, 2980, 2871, 2889, 2200, 1655, 1604; ^1H NMR (500 MHz, CDCl_3) δ_{H} : 7.58–7.53 (2H, m), 7.47–7.42 (1H, m), 7.41–7.36 (2H, m), 5.72 (1H, d, $J = 2.5$ Hz), 3.39 (1H, app. sex, $J = 6.7$ Hz), 2.87 (1H, dd, $J = 15.3, 6.7$ Hz), 2.81 (1H, dd, $J = 15.3, 7.9$ Hz), 2.20 (3H, s), 2.19 (3H, s), 1.25 (3H, d, $J = 6.7$ Hz); ^{13}C NMR (125 MHz, CDCl_3) δ : 187.8, 133.0, 130.6, 128.6, 125.3, 123.1, 121.0, 120.2, 103.7, 90.5, 88.2, 54.3, 27.5, 22.2, 13.0, 11.1; HRMS (ESI, +ve) m/z : calcd. for $\text{C}_{18}\text{H}_{19}\text{NONa}$: 288.1364, found: 288.1373 [$\text{M} + \text{Na}$] $^+$.

Trimethyl((4-(trifluoromethyl)phenyl)ethynyl)silane¹³⁴ (176)

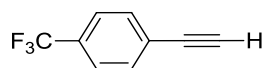


In a two-necked flask, a solution of 1-bromo-4-(trifluoromethyl)benzene (900 mg, 4.00 mmol, 1 equiv.), bis(triphenylphosphine)palladium(II) dichloride (84 mg, 0.12 mmol, 3 mol%), copper(I) iodide (46 mg, 0.24 mmol, 6 mol%), triphenylphosphine (63 mg, 0.24 mmol, 6 mol%) in pyridine (15 mL) was heated to 80 °C. Ethynyltrimethylsilane (737 μ L, 5.33 mmol, 1.33 equiv.) was added dropwise under a positive pressure of nitrogen and the reaction was allowed to stir for 24 hours. Upon completion the reaction was cooled to RT, quenched with NH_4Cl (sat) (50 mL) and extracted with DCM (3×50 mL). The organic extracts are then washed with water (3×50 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The crude material was subjected to flash chromatography, eluting with 100% Pet, to give **176** as a pale yellow oil (871 mg, 90%).

^1H NMR (CDCl_3 , 300 MHz) δ : 7.36 (4H, s), 0.07 (9H, s); ^{13}C NMR (CDCl_3 , 75 MHz) δ : 132.4, 130.4 (q, $J = 32.8$ Hz), 127.2 (m), 125.3 (q, $J = 3.8$ Hz), 124.1 (q, $J = 272.4$ Hz), 103.6, 97.4, 0.0.

All other data in accordance with literature precedence.¹³⁴

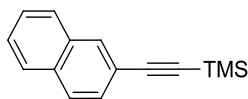
1-Ethynyl-4-(trifluoromethyl)benzene¹³⁵ (**177**)



To **175** (1.95 g, 8.08 mmol, 1 equiv.) in a round-bottomed flask was added MeOH (20 mL) and NaOH solution (1.43 M, 20 mL). The reaction was allowed to stir for 24 hours at room temperature. Upon completion, pentane (20 mL) was added to the reaction mixture and organics extracted. The organic extract was then washed with water (20 mL), dried over MgSO_4 and concentrated *in vacuo*. The crude product was distilled under reduced pressure (34 – 35 °C at 6 mmHg) to afford **177** as a clear oil (206 mg, 15%).

^1H NMR (CDCl_3 , 500 MHz) δ_{H} : 7.61 (4H, s), 3.21 (1H, s); ^{13}C NMR (CDCl_3 , 125 MHz) δ_{C} : 132.4, 130.6 (q, $J = 32.4$), 125.9 (m), 125.3 (q, $J = 3.5$ Hz), 123.8 (q, $J = 272.6$ Hz), 82.2, 79.6.

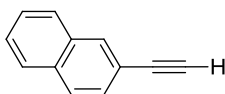
All other data in accordance with literature precedence.¹³⁵

Trimethyl(naphthalen-2-ylethynyl)silane¹³⁶ (179)

2-bromonaphthalene (2.00 g, 9.66 mmol, 1 equiv.), bis(triphenylphosphine)palladium(II) dichloride (302 mg, 0.43 mmol, 4.5 mol%) and copper(I) iodide (91 mg, 0.48 mmol, 5 mol%) were added to a round-bottomed flask and purged with nitrogen. Distilled triethylamine (40 mL) was added, followed by the dropwise addition of ethynyltrimethylsilane (2.00 mL, 14.49 mmol, 1.5 equiv.). The reaction was stirred at RT for 16 hours, then quenched with NH₄Cl (sat) (40 mL) and extracted with hexane (3 × 40 mL). The organic extracts were combined and dried over Na₂SO₄ and concentrated *in vacuo*. The crude product was subjected to flash chromatography, eluting with 100% Pet, to afford **179** as a clear oil (1.38 g, 64%).

¹H NMR (CDCl₃, 300 MHz) δ_{H} : 7.91 (1H, app.s), 7.76–7.62 (3H, m), 7.46–7.33 (3H, m), 0.20 (9H, s); ¹³C NMR (CDCl₃, 75 MHz) δ_{C} : 132.9, 132.8, 132.0, 128.6, 127.8, 127.8, 127.7, 126.7, 126.5, 120.4, 105.4, 94.5, 0.0.

All other data in accordance with literature precedence.¹³⁶

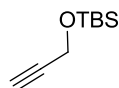
2-Ethynylnaphthalene¹³⁶ (180)

To a degassed solution of potassium hydroxide (375 mg, 6.70 mmol, 2 equiv.) in MeOH (12.5 mL) was added a solution of **179** (750 mg, 3.35 mmol, 1 equiv.) in DCM (12.5 mL) dropwise. The reaction was allowed to stir for 2 hours, then quenched with water (10 mL) and the organic layer extracted. The organic extract was dried over Na₂SO₄ and concentrated *in vacuo* before being subjected to flash chromatography, eluting with 100% Pet, to afford **180** as a clear oil (296 mg, 58%).

^1H NMR (CDCl_3 , 300 MHz) δ : 7.87 (1H, app.s), 7.70–7.57 (3H, m), 7.41–7.29 (3H, m), 2.98 (1H, s); ^{13}C NMR (CDCl_3 , 75 MHz) δ : 133.1, 132.8, 132.3, 128.6, 128.0, 127.8, 127.8, 126.9, 126.6, 119.4, 84.0, 77.2.

All other data in accordance with literature precedence.¹³⁶

***tert*-Butyldimethyl(prop-2-yn-1-yloxy)silane¹³⁷ (**182**)**

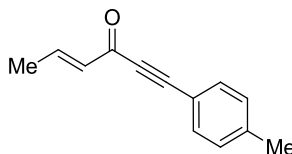


To a solution of propargylic alcohol (1.00 mL, 17.80 mmol, 1 equiv.) in THF (35 mL) was added triethylamine (4.90 mL, 35.60 mmol, 2 equiv.), TBSCl (2.68 g, 17.80 mmol, 1 equiv.) and DMAP (110 mg, 0.90 mmol, 20 mol %). The resultant mixture was stirred at rt for 18 h, diluted with hexane (150 mL) and washed with NH_4Cl (sat) (150 mL) and brine (150 mL) and dried over MgSO_4 , filtered and concentrated *in vacuo*. Purification via flash chromatography, eluting with 100 % Pet, afforded **182** as a clear oil (2.97 g, 98 %).

^1H NMR (500 MHz, CDCl_3) δ_{H} : 4.33 (2H, d, $J = 2.5$ Hz), 2.40 (1H, t, $J = 2.5$ Hz), 0.93 (9H, s), 0.14 (6H, s); ^{13}C NMR (125 MHz, CDCl_3) δ_{C} : 82.4, 72.8, 51.5, 25.8, 18.3, -5.2.

All other data in accordance with literature precedence.¹⁸⁹

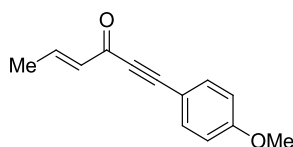
(*E*)-1-(*p*-Tolyl)hex-4-en-1-yn-3-one (183**)**



Prepared according to general procedure A, using 1-ethynyl-4-methylbenzene (1.02 mL, 8.00 mmol, 1 equiv.), crotonaldehyde (663 μL , 8.00 mmol, 1 equiv.), $n\text{-BuLi}$ (1.6 M in Hex., 5.50 mL, 8.80 mmol, 1.1 equiv.), manganese dioxide (17.39 g, 200 mmol, 25 equiv.). Purified by flash chromatography to afford **183** as a yellow oil (893 mg, 60 %).

FTIR (thin film) ν_{max} : 3035, 2964, 2909, 2203, 1641, 1615, 1603, 1509; ^1H NMR (300 MHz, CDCl_3) δ_{H} : 7.41 (2H, app.d, $J = 8.2$ Hz), 7.28–7.14 (1H, m), 7.11 (2H, app.d, $J = 8.2$ Hz), 6.18 (1H, dq, $J = 15.7, 1.6$ Hz), 2.31 (3H, s), 1.94 (3H, dd, $J = 6.9, 1.6$ Hz); ^{13}C NMR (75 MHz) δ : 178.5, 149.2, 141.2, 134.0, 132.9, 129.4, 117.1, 91.7, 86.1, 21.7, 18.5; HRMS (ESI, +ve) m/z : calcd. for $\text{C}_{13}\text{H}_{12}\text{ONa}$: 207.0786, found: 207.0782 $[\text{M} + \text{Na}]^+$.

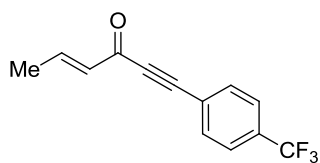
(*E*)-1-(4-Methoxyphenyl)hex-4-en-1-yn-3-one (184)



Prepared according to general procedure A, using 4-ethynylanisole (0.98 mL, 7.56 mmol, 1 equiv.), crotonaldehyde (0.62 mL, 7.56 mmol, 1 equiv.), $n\text{BuLi}$ (1.6M in Hex., 5.20 mL, 8.32 mmol, 1.1 equiv.), THF (50 mL), manganese dioxide (13.0 g, 150 mmol, 25 equiv.), DCM (50 mL). Purification was achieved by flash chromatography to afford **184** as a yellow oil (0.62 g, 52%).

FTIR (thin film) ν_{max} : 2938, 2841, 2201, 1735, 1643, 1619, 1599, 1568; ^1H NMR (500 MHz, CDCl_3) δ_{H} : 7.57 (1H, app. d, $J = 8.8$ Hz), 7.31–7.24 (1H, m), 6.92 (2H, app. d, $J = 8.8$ Hz), 6.27 (1H, d, $J = 15.5$ Hz), 3.86 (3H, s), 2.03 (3H, d, $J = 6.9$ Hz); ^{13}C NMR (125 MHz, CDCl_3) δ : 178.5, 161.5, 148.8, 134.9, 134.0, 114.3, 112.0, 92.1, 86.1, 55.4, 18.4; HRMS (ESI, +ve) m/z : calcd. for $\text{C}_{13}\text{H}_{12}\text{O}_2\text{Na}$ 223.0735 found 223.0734 $[\text{M} + \text{Na}]^+$.

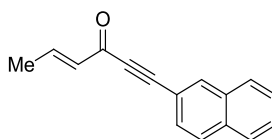
(*E*)-1-(4-(Trifluoromethyl)phenyl)hex-4-en-1-yn-3-one (185)



Prepared according to general procedure A, using 1-ethynyl-4-(trifluoromethyl)benzene (1.36 g, 8.00 mmol, 1 equiv.), crotonaldehyde (663 μ L, 8.00 mmol, 1 equiv.), n BuLi (1.6 M in Hex., 5.50 mL, 8.80 mmol, 1.1 equiv.), manganese dioxide (17.39 g, 200 mmol, 25 equiv.). Crude residue purified by washing with petroleum ether (5 mL) to afford **185** as a light yellow solid (302 mg, 16 %).

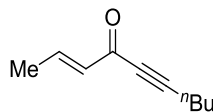
FTIR (thin film) ν_{max} : 2981, 2212, 1644, 1621; ^1H NMR (500 MHz, CDCl_3) δ_{H} : 7.71 (2H, app.d., $J = 8.2$ Hz), 7.66 (2H, app.d., $J = 8.2$ Hz), 7.31 (1H, dq, $J = 15.9, 6.9$ Hz), 6.29 (1H, dq, $J = 15.9, 1.6$ Hz), 2.05 (3H, dd, $J = 6.9, 1.6$ Hz); ^{13}C NMR (100 MHz) δ_{C} : 177.9, 150.3, 133.8, 133.0, 132.0 (q, $J = 32.9$), 125.6 (q, $J = 3.7$ Hz), 124.1, 123.6 (q, $J = 272.9$ Hz), 88.6, 87.5, 18.6; HRMS (ESI, +ve) m/z : calcd. for $\text{C}_{13}\text{H}_9\text{F}_3\text{ONa}$: 261.0503, found: 261.0476 $[\text{M} + \text{Na}]^+$.

(*E*)-1-(Naphthalen-2-yl)hex-4-en-1-yn-3-one (186)



Prepared according to general procedure A, using 2-ethynylnaphthalene (272 mg, 1.80 mmol, 1 equiv.), crotonaldehyde (148 μ L, 1.80 mmol, 1 equiv.), n BuLi (1.6 M in Hex., 1.23 mL, 2.00 mmol, 1.1 equiv.), manganese dioxide (3.89 g, 44.8 mmol, 25 equiv.). Purified by flash chromatography to afford **186** as a yellow oil (220 mg, 56%).

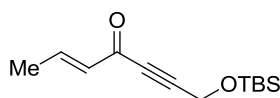
FTIR (thin film) ν_{max} : 2981, 2889, 2188, 1645, 1618; ^1H NMR (400 MHz, CDCl_3) δ_{H} : 8.22 (1H, s), 7.94–7.85 (3H, m), 7.67–7.54 (3H, m), 7.41 (1H, dq, $J = 15.7, 6.8$ Hz), 6.36 (1H, dq, $J = 15.7, 1.6$ Hz), 2.11 (3H, dd, $J = 6.8, 1.6$ Hz); ^{13}C NMR (100 MHz) δ : 178.4, 149.5, 134.1, 133.8, 132.8, 129.0, 128.5, 128.4, 127.9, 127.9, 127.0, 117.4, 91.6, 86.5, 18.6; HRMS (ESI, +ve) m/z : calcd. for $\text{C}_{16}\text{H}_{12}\text{ONa}$: 243.0786, found: 243.0781 $[\text{M} + \text{Na}]^+$.

(E)-Dec-2-en-5-yn-4-one (187)

Prepared according to general procedure A, using 1-hexyne (1.12 mL, 9.79 mmol, 1 equiv.), crotonaldehyde (0.80 mL, 9.79 mmol, 1 equiv.), *n*BuLi (1.6 M in Hex., 6.70 mL, 10.7 mmol, 1.1 equiv.), THF (150 mL), manganese dioxide (10.1 g, 115.9 mmol, 25 equiv.), DCM (150 mL). Purification was achieved by flash chromatography to afford **187** as a pale yellow oil (0.70 g, 48%).

^1H NMR (400 MHz, CDCl_3) δ_{H} : 7.20 (1H, dq, $J = 15.8, 6.9$ Hz), 7.15 (1H, dq, $J = 15.8, 6.9$ Hz), 6.17 (1H, d, $J = 15.8$ Hz), 2.41 (2H, t, $J = 7.3$ Hz), 1.99 (3H, d, $J = 6.9$ Hz), 1.63–1.43 (4H, m), 0.95 (3H, t, $J = 7.3$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ : 178.8, 145.0, 134.0, 94.5, 79.0, 29.9, 22.0, 18.7, 18.3, 13.5.

All data is in accordance to reported literature values.¹⁹⁰

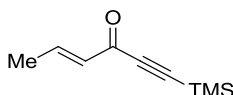
(E)-7-((*tert*-Butyldimethylsilyl)oxy)hept-2-en-5-yn-4-one (188)

Prepared according to general procedure A, using *tert*-butyldimethyl(prop-2-yn-1-yloxy)silane (0.69g, 4.10 mmol, 1 equiv.), crotonaldehyde (0.38 mL, 4.10 mmol, 1 equiv.), *n*BuLi (1.6 M in Hex., 2.5 mL, 4.50 mmol, 1.1 equiv.), THF (45 mL), manganese dioxide (7.20 g, 83.0 mmol, 25 equiv.), DCM (20 mL). Purification was achieved by flash chromatography to afford **188** as a yellow oil (0.51 g, 65%).

FTIR (thin film) ν_{max} : 2956, 2930, 2858, 2217, 1647, 1630; ^1H NMR (400 MHz, CDCl_3) δ_{H} : 7.16 (1H, dq, $J = 15.4, 7.1$ Hz), 6.13 (1H, d, $J = 15.4$ Hz), 4.46 (2H, s), 1.94 (3H, d, $J = 7.1$ Hz), 0.88 (9H, s); ^{13}C NMR (100 MHz) δ_{C} : 177.8, 149.9, 133.6, 90.6,

82.0, 51.5, 25.6, 18.3, 18.2, -5.3; HRMS (ESI, +ve) m/z : calcd. for $C_{13}H_{22}O_2SiNa$: 261.1287, found: 261.1285 $[M + Na]^+$.

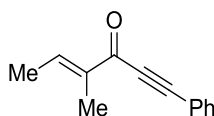
(E)-1-(trimethylsilyl)hex-4-en-1-yn-3-one (189)



Prepared according to general procedure A, using ethynyltrimethylsilane (1.38 mL, 9.79 mmol, 1 equiv.), crotonaldehyde (800 μ L, 9.79 mmol, 1 equiv.), n BuLi (1.6 M in Hex., 6.70 mL, 10.7 mmol, 1.1 equiv.), manganese dioxide (21.2 g, 244 mmol, 25 equiv.). Purified by flash chromatography to afford **189** as a pale yellow oil (830 mg, 51%).

FTIR (thin film) ν_{max} : 2962, 2903, 2159, 1639, 1626; ^1H NMR (300 MHz, CDCl_3) δ_{H} : 7.20 (1H, dq, $J = 15.7, 6.9$ Hz), 6.18 (1H, dq, $J = 15.7, 1.7$ Hz), 1.96 (3H, dd, $J = 6.9, 1.7$ Hz), 0.26 (9H, s); ^{13}C NMR (125 MHz) δ_{C} : 178.1, 150.0, 133.7, 100.3, 98.1, 18.5, -0.68; HRMS (ESI, +ve) m/z : calcd. for $C_9H_{15}OSi$: 167.0892, found: 167.0872 $[M + H]^+$.

(E)-4-Methyl-1-phenylhex-4-en-1-yn-3-one (190)

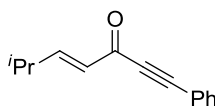


Prepared according to general procedure A, using phenylacetylene (653 μ L, 5.94 mmol, 1 equiv.), (*E*)-2-methylbut-2-enal (574 μ L, 5.94 mmol, 1 equiv.), n BuLi (1.6 M in Hex., 4.01 mL, 6.53 mmol, 1.1 equiv.), manganese dioxide (12.9 g, 149 mmol, 25 equiv.). Purified by flash chromatography to afford **190** as a yellow oil (623 mg, 57%).

FTIR (thin film) ν_{max} : 2980, 2194, 1622, 1578; ^1H NMR (500 MHz, CDCl_3) δ_{H} : 7.60 (2H, app. d, $J = 8.4$ Hz), 7.47–7.42 (1H, m), 7.41–7.30 (3H, m), 1.99 (3H, d, $J = 7.2$ Hz), 1.87 (3H, s); ^{13}C NMR (125 MHz) δ_{C} : 180.2, 145.2, 139.5, 132.7, 130.3, 128.6,

120.5, 90.9, 86.1, 15.2, 10.3; HRMS (ESI, +ve) m/z : calcd. for $C_{13}H_{12}ONa$: 207.0786, found: 207.0777 $[M + Na]^+$.

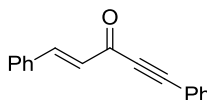
(E)-6-Methyl-1-phenylhept-4-en-1-yn-3-one (191)



Prepared according to general procedure A, using phenyl acetylene (1.07 mL, 9.79 mmol, 1 equiv.), 4-methyl-2-pentenal (1.14 mL, 9.79 mmol, 1 equiv.), n BuLi (1.6M in Hex., 6.7 mL, 10.7 mmol, 1.1 equiv.), THF (150 mL), manganese dioxide (18.0 g, 208.0 mmol, 25 equiv.), DCM (150 mL). Purification was achieved by flash chromatography to afford **191** as a pale yellow oil (1.31 g, 58%).

FTIR (thin film) ν_{\max} : 2964, 2871, 2210, 1642, 1620; 1H NMR (400 MHz, $CDCl_3$) δ_H : 7.64–7.61 (2H, m), 7.48–7.39 (3H, m), 7.24 (1H, dd, $J = 15.9, 6.7$ Hz), 6.22 (1H, dd, $J = 15.9, 1.5$ Hz), 2.61 (1H, doct, $J = 6.9, 1.5$ Hz), 1.16 (6H, d, $J = 6.9$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C : 178.9, 160.1, 132.9, 130.5, 129.7, 128.6, 120.3, 91.1, 86.4, 31.4, 21.2; HRMS (ESI, +ve) m/z : calcd. for $C_{14}H_{15}O$ 199.1123 found 199.1120 $[M + H]^+$.

(E)-1,5-Diphenylpent-1-en-4-yn-3-one (192)

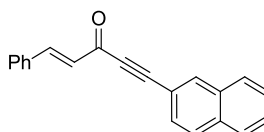


Prepared according to general procedure A, using phenyl acetylene (1.07 mL, 9.79 mmol, 1 equiv.), cinnamaldehyde (1.23 mL, 9.79 mmol, 1 equiv.), n BuLi (1.6M in Hex., 6.70 mL, 10.7 mmol, 1.1 equiv.), THF (150 mL), manganese dioxide (11.3 g, 130 mmol, 25 equiv.), DCM (150 mL). Purification was achieved by flash chromatography (8:1 Pet/EtOAc) to afford a pale yellow solid. Recrystallisation (Pet.) afforded **192** as colourless needles (1.31 g, 58%).

MP: 75–77 °C. ^1H NMR (400 MHz, CDCl_3) δ_{H} : 7.92 (1H, d, $J = 16.1$ Hz), 7.67–7.59 (4H, m), 7.50–7.41 (6H, m), 6.88 (1H, d, $J = 16.1$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ_{C} : 178.2, 148.3, 134.1, 132.9, 131.2, 130.6, 129.1, 128.7, 128.7, 128.6, 120.3, 91.6, 86.7.

All analytical data in accordance to reported values.¹⁹¹

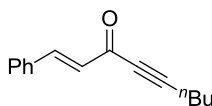
(*E*)-5-(Naphthalen-2-yl)-1-phenylpent-1-en-4-yn-3-one (193)



Prepared according to general procedure A, using 2-ethynylnaphthalene (146 mg, 0.96 mmol, 1 equiv.), cinnamaldehyde (121 μL , 0.96 mmol, 1 equiv.), $n\text{BuLi}$ (1.6 M in Hex., 661 μL , 1.06 mmol, 1.1 equiv.), manganese dioxide (2.01 g, 24.0 mmol, 25 equiv.). Purified by flash chromatography to afford **193** as a yellow oil (147 mg, 54%).

FTIR (thin film) ν_{max} : 3057, 2186, 1626, 1593, 1575; ^1H NMR (500 MHz, CDCl_3) δ_{H} : 8.24 (1H, s), 7.99 (1H, d, $J = 16.1$ Hz), 7.93–7.85 (3H, m), 7.69–7.63 (3H, m), 7.60–7.57 (2H, m), 7.50–7.44 (3H, m), 6.93 (1H, d, $J = 16.1$ Hz); ^{13}C NMR (125 MHz) δ_{C} : 178.2, 148.3, 134.1, 133.9, 132.7, 131.2, 130.3, 129.1, 128.7, 128.6, 128.5, 128.4, 128.2, 128.0, 127.9, 127.0, 117.4, 92.1, 86.9; HRMS (ESI, +ve) m/z : calcd. for $\text{C}_{21}\text{H}_{15}\text{O}$: 283.1123; found, 283.1116 $[\text{M} + \text{H}]^+$.

(*E*)-1-Phenylnon-1-en-4-yn-3-one (194)



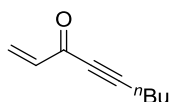
Prepared according to general procedure A, using 1-hexyne (1.12 mL, 9.79 mmol, 1 equiv.), cinnamaldehyde (1.23 mL, 9.79 mmol, 1 equiv.), $n\text{BuLi}$ (1.6M in Hex., 6.7 mL, 10.7 mmol, 1.1 equiv.), THF (150 mL), manganese dioxide (8.93 g, 102.8 mmol, 25

equiv.), DCM (150 mL). Purification was achieved by flash chromatography to afford **194** as a pale yellow oil (0.88 g, 42%).

FTIR (thin film) ν_{max} : 2959, 2933, 2873, 2210, 1628; ^1H NMR (300 MHz, CDCl_3) δ_{H} : 7.70 (1H, d, $J = 16.3$ Hz), 7.50–7.41 (2H, m), 7.36–7.26 (3H, m), 6.66 (1H, d, $J = 16.3$ Hz), 2.37 (2H, t, $J = 6.9$ Hz), 1.62–1.49 (2H, m), 1.48–1.34 (2H, m), 0.88 (3H, t, $J = 6.9$ Hz); ^{13}C NMR (75 MHz, CDCl_3) δ_{C} : 178.6, 148.1, 134.2, 131.0, 129.1, 128.7, 128.6, 95.0, 79.3, 29.9, 22.0, 18.7, 13.6; HRMS (ESI, +ve) m/z : calcd. for $\text{C}_{15}\text{H}_{17}\text{O}$ 213.1279 found 213.1253 $[\text{M} + \text{H}]^+$.

All analytical data in accordance to reported values.¹⁹²

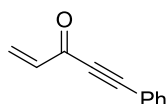
Non-1-en-4-yn-3-one (195)



Prepared according to general procedure A, using hexyne (540 μL , 4.90 mmol, 1 equiv.), acrolein (330 μL , 4.90 mmol, 1 equiv.), $n\text{BuLi}$ (1.6M in Hex., 3.35 mL, 5.35 mmol, 1.1 equiv.), THF (50 mL), manganese dioxide (10.1 g, 116 mmol, 25 equiv.), DCM (50 mL). Purification was achieved by flash chromatography to afford **195** as a pale yellow oil (0.30 g, 44%).

FTIR (thin film) ν_{max} : 2960, 2933, 2874, 2216, 1646, 1611; ^1H NMR (500 MHz, CDCl_3) δ_{H} : 6.53 (1H, app. d, $J = 16.8$ Hz), 6.39 (1H, dd, $J = 16.8, 10.5$ Hz), 6.16 (1H, d, $J = 10.5$ Hz), 2.43 (2H, t, $J = 7.1$ Hz), 1.64–1.59 (2H, m), 1.51–1.44 (2H, m), 0.95 (3H, t, $J = 7.4$ Hz); ^{13}C NMR (125 MHz, CDCl_3) δ_{C} : 179.2, 138.1, 133.2, 95.7, 78.6, 29.8, 22.0, 18.7, 13.5; HRMS (ESI, +ve) m/z : calcd. for $\text{C}_9\text{H}_{13}\text{O}$ 137.0966 found 137.0942 $[\text{M} + \text{H}]^+$.

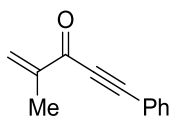
5-Phenylpent-1-en-4-yn-3-one (196)



Prepared according to general procedure A, using phenyl acetylene (540 μ L, 4.90 mmol, 1 equiv.), acrolein (330 μ L, 4.90 mmol, 1 equiv.), n BuLi (1.6M in Hex., 3.35 mL, 5.35 mmol, 1.1 equiv.), THF (50 mL), manganese dioxide (10.1 g, 116.4 mmol, 25 equiv.), DCM (50 mL). Purification was achieved by flash chromatography to afford **196** as a pale yellow oil (0.36 g, 48%).

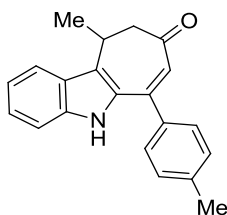
FTIR (thin film) ν_{max} : 3061, 2202, 1638, 1607; ^1H NMR (500 MHz, CDCl_3) δ_{H} : 7.62 (2H, d, $J = 7.7$ Hz), 7.48 (1H, app. t, $J = 7.7$ Hz), 7.41 (2H, t, $J = 7.7$ Hz), 6.67 (1H, d, $J = 17.4$ Hz), 6.50 (1H, dd, $J = 17.4, 10.1$ Hz), 6.24 (1H, d, $J = 10.1$ Hz); ^{13}C NMR (125 MHz, CDCl_3) δ_{C} : 178.8, 138.0, 133.5, 133.0, 130.8, 128.7, 119.7, 92.1, 85.8; HRMS (ESI, +ve) m/z : calcd. for $\text{C}_{11}\text{H}_8\text{ONa}$ 179.0473 found 179.0466 $[\text{M} + \text{Na}]^+$.

2-Methyl-5-phenylpent-1-en-4-yn-3-one (197)



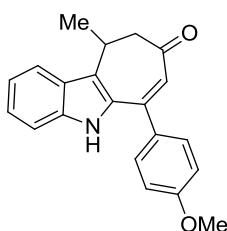
Prepared according to general procedure A, using phenylacetylene (653 μ L, 5.90 mmol, 1 equiv.), methacrolein (490 μ L, 5.90 mmol, 1 equiv.), n BuLi (1.6 M in Hex., 4.01 mL, 6.50 mmol, 1.1 equiv.), manganese dioxide (12.9 g, 149 mmol, 25 equiv.). Purification by flash chromatography afforded **197** as an amorphous white solid (552 mg, 55 %).

FTIR (thin film) ν_{max} : 2981, 2921, 2205, 1632, 1593; ^1H NMR (500 MHz, CDCl_3) δ_{H} : 7.60 (2H, app. d, $J = 7.6$ Hz), 7.45 (1H, app. t, $J = 7.6$ Hz), 7.39 (2H, app. t, $J = 7.6$ Hz), 6.55 (1H, s), 6.08 (1H, s), 1.97 (3H, s); ^{13}C NMR (125 MHz) δ_{C} : 180.1, 145.3, 132.9, 130.7, 130.5, 128.6, 120.3, 91.4, 86.0, 16.2; HRMS (ESI, +ve) m/z : calcd. for $\text{C}_{12}\text{H}_{10}\text{ONa}$: 193.0629, found: 193.0614 $[\text{M} + \text{Na}]^+$.

10-Methyl-6-(p-tolyl)-9,10-dihydrocyclohepta[b]indol-8(5H)-one (198)

Prepared according to general procedure B (reaction time = 6 h), using indole (33 mg, 0.28 mmol, 1.05 equiv.), **183** (50 mg, 0.27 mmol, 1 equiv.), sodium tetrachloroaurate (III) hydrate (5 mg, 0.01 mmol, 5 mol%), acetonitrile (2 mL). Purification was achieved by flash chromatography to afford **198** as a yellow oil (79 mg, 98 %).

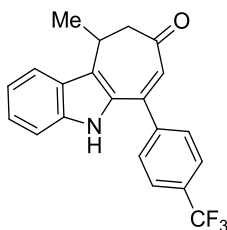
FTIR (thin film) ν_{max} : 3058, 3022, 2946, 2926, 1718, 1615, 1529. ^1H NMR (500 MHz, CDCl_3) δ_{H} : 7.89 (1H, s), 7.69 (1H, app.d., $J = 8.1$ Hz), 7.37 (2H, app.d., $J = 8.8$ Hz), 7.32 (2H, app.d., $J = 8.8$ Hz), 7.30–7.23 (2H, m), 7.23–7.12 (1H, m), 6.19 (1H, s), 3.70–3.57 (1H, m), 3.18 (1H, dd, $J = 14.9, 3.1$ Hz), 2.95 (1H, dd, $J = 14.9, 5.2$ Hz), 2.47 (3H, s), 1.37 (3H, d, $J = 7.4$ Hz); ^{13}C NMR (125 MHz) δ_{C} : 199.9, 145.3, 139.4, 136.8, 135.5, 130.0, 129.6, 128.6, 28.5, 126.8, 126.0, 124.6, 120.3, 199.4, 111.4, 48.3, 25.0, 21.3, 17.0; HRMS (ESI, +ve) m/z : calcd. for $\text{C}_{21}\text{H}_{20}\text{NO}$: 302.1545, found: 302.1549 $[\text{M} + \text{H}]^+$.

6-(4-Methoxyphenyl)-10-methyl-9,10-dihydrocyclohepta[b]indol-8(5H)-one (199)

Prepared according to general procedure B (reaction time = 24 h), using indole (43 mg, 0.42 mmol, 1.05 equiv.), **184** (80 mg, 0.40 mmol, 1 equiv.), sodium tetrachloroaurate (III) hydrate (8 mg, 0.02 mmol, 5 mol%), acetonitrile (2 mL). Purification was achieved by flash chromatography to afford a yellow solid. Recrystallization from DCM/Pet. afforded **199** as yellow needles (111 mg, 82%).

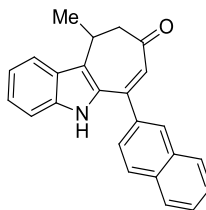
MP: 166–167 °C; FTIR (thin film) ν_{max} : 2956, 2928, 2835, 1636, 1604; ^1H NMR (500 MHz, CDCl_3) δ_{H} : 7.78 (1H, br. s), 7.68 (1H, d, $J = 8.1$ Hz), 7.41 (2H, app. d, $J = 8.5$ Hz), 7.29–7.16 (3H, m), 7.03 (2H, app. d, $J = 8.5$ Hz), 6.20 (1H, s), 3.67–3.59 (1H, m), 3.17 (1H, dd, $J = 14.6, 2.9$ Hz), 2.95 (1H, dd, $J = 14.6, 4.9$ Hz), 1.37 (3H, d, $J = 7.4$ Hz); ^{13}C NMR (125 MHz, CDCl_3) δ_{C} : 199.9, 160.5, 144.9, 135.4, 131.9, 130.2, 130.1, 128.5, 126.8, 126.0, 124.6, 120.4, 119.4, 114.4, 111.3, 55.5, 48.4, 24.9, 16.9; HRMS (ESI, +ve) m/z : calcd. for $\text{C}_{21}\text{H}_{19}\text{NO}_2\text{Na}$ 340.1313 found 340.1321 $[\text{M} + \text{H}]^+$.

10-Methyl-6-(4-(trifluoromethyl)phenyl)-9,10-dihydrocyclohepta[b]indol-8(5H)-one (200)



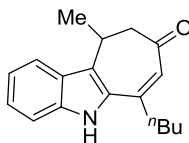
Prepared according to general procedure B (reaction time = 16 h), using indole (26 mg, 0.22 mmol, 1.05 equiv.), **185** (50mg, 0.21 mmol, 1 equiv.), acetonitrile (2 mL). Purification was achieved by flash chromatography to afford **200** as a yellow solid (54 mg, 73 %).

MP: 216–217 °C; FTIR (thin film) ν_{max} : 3361, 2981, 2972, 1890, 1638, 1580, 1532; ^1H NMR (400 MHz, CDCl_3) δ_{H} : 7.83 (2H, app.d., $J = 8.1$ Hz), 7.73 (2H, app.d., $J = 7.6$ Hz), 7.65 (2H, app.d., $J = 8.1$ Hz), 7.37–7.29 (2H, m), 7.28–7.18 (1H, m), 6.20 (1H, s), 3.76–3.62 (1H, m), 3.23 (1H, dd, $J = 14.7, 2.9$ Hz), 3.01 (1H, dd, $J = 14.7, 5.2$ Hz), 1.40 (3H, d, $J = 7.5$ Hz); ^{13}C NMR (100 MHz) δ : 199.5, 143.7, 143.3, 135.8, 131.4 (q, $J = 32.7$ Hz), 129.3, 129.1, 129.0, 126.8, 126.8, 126.1 (q, $J = 3.3$ Hz), 125.1, 123.9 (q, $J = 272.2$), 120.7, 119.6, 111.5, 48.1, 25.0, 17.1; HRMS (ESI, +ve) m/z : calcd. for $\text{C}_{21}\text{H}_{17}\text{F}_3\text{NO}$: 356.1262, found: 356.1256 $[\text{M} + \text{H}]^+$.

10-Methyl-6-(naphthalen-2-yl)-9,10-dihydrocyclohepta[b]indol-8(5H)-one (201)

Prepared according to general procedure B (reaction time = 8 h, RT), using indole (22 mg, 0.19 mmol, 1.05 equiv.), **186** (40 mg, 0.18 mmol, 1 equiv.), sodium tetrachloroaurate (III) hydrate (3.6 mg, 0.01 mmol, 5 mol%), acetonitrile (2 mL). Purification was achieved by flash chromatography afforded **201** as a yellow oil (50 mg, 81%).

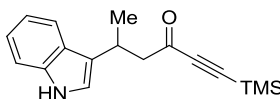
FTIR (thin film) ν_{max} : 3319, 3056, 2957, 2924, 2855, 1623, 1567, 1536; ^1H NMR (300 MHz, CDCl_3) δ_{H} : 7.91–7.72 (5H, m), 7.60 (1H, app.d., $J = 7.9$ Hz), 7.55–7.41 (3H, m), 7.22–7.03 (3H, m), 6.18 (1H, d, $J = 1.5$ Hz), 3.64–3.48 (1H, m), 3.11 (1H, dd, $J = 14.6, 3.3$ Hz), 2.87 (1H, ddd, $J = 14.6, 5.4, 1.5$ Hz), 1.29 (3H, d, $J = 7.4$ Hz); ^{13}C NMR (75 MHz, CDCl_3) δ_{C} : 199.9, 145.3, 137.1, 135.6, 133.4, 133.1, 130.1, 129.1, 128.8, 128.4, 128.0, 127.9, 127.2, 127.0, 126.8, 126.3, 126.1, 124.7, 120.5, 119.5, 111.5, 48.3, 25.0, 17.1; HRMS (ESI, +ve) m/z : calcd. for $\text{C}_{24}\text{H}_{20}\text{NO}$: 388.1545, found, 338.1553 [$\text{M} + \text{H}$] $^+$.

6-Butyl-10-methyl-9,10-dihydrocyclohepta[b]indol-8(5H)-one (202)

Prepared according to general procedure B (reaction time = 24 h, reflux), using indole (43 mg, 0.42 mmol, 1.05 equiv.), **187** (60 mg, 0.4 mmol, 1 equiv.), sodium tetrachloroaurate (III) hydrate (8 mg, 0.02 mmol, 5 mol%) in acetonitrile (2 mL). Purification was achieved by flash chromatography to afford **202** a yellow oil (85 mg, 79%).

FTIR (thin film) ν_{\max} : 2915, 2843, 1704, 1692, 1622, 1602; ^1H NMR (500 MHz, CDCl_3) δ_{H} : 8.15 (1H, br. s), 7.64 (1H, d, $J = 8.3$ Hz), 7.42–7.40 (1H, m), 7.32–7.28 (1H, m), 7.18 (1H, t, $J = 7.3$ Hz), 6.15 (1H, s), 3.07 (1H, dd, $J = 14.2, 3.1$ Hz), 2.87 (1H, dd, $J = 14.2, 5.5$ Hz), 2.74–2.58 (2H, m), 1.67 (2H, pent, $J = 7.2$ Hz), 1.47 (2H, sext, $J = 7.2$ Hz), 1.23 (3H, d, $J = 7.2$ Hz), 0.98 (3H, t, $J = 7.2$ Hz); ^{13}C NMR (125 MHz, CDCl_3) δ : 200.2, 144.7, 141.3, 127.8, 126.8, 125.7, 124.6, 120.4, 119.4, 111.2, 47.7, 36.2, 31.3, 22.5, 16.6, 13.9; HRMS (ESI, +ve) m/z : calcd. for $\text{C}_{18}\text{H}_{21}\text{ONNa}$ 290.1521 found 290.1523 $[\text{M} + \text{Na}]^+$.

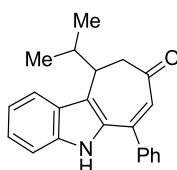
5-(1H-Indol-3-yl)-1-(trimethylsilyl)hex-1-yn-3-one (204)



Prepared according to general procedure B (reaction time = 48 h, reflux), using indole (43 μL , 0.42 mmol, 1.05 equiv.), **189** (66 mg, 0.40 mmol, 1 equiv.), sodium tetrachloroaurate (III) hydrate (8 mg, 0.020 mmol, 5 mol%), acetonitrile (2 mL). Purification by flash chromatography afforded **204** as a yellow oil (111 mg, 98%).

FTIR (thin film) ν_{\max} : 3058, 2961, 2149, 1665, 1620. ^1H NMR (400 MHz, CDCl_3) δ_{H} : 8.08 (1H, br.s), 7.74–7.71 (1H, m), 7.41 (1H, dt, $J = 8.2, 0.9$ Hz), 7.28–7.17 (2H, m), 7.03 (1H, d, $J = 2.2$ Hz), 3.87–3.79 (1H, m), 3.14 (1H, dd, $J = 16.0, 5.7$ Hz), 2.88 (1H, dd, $J = 16.0, 8.9$ Hz), 1.48 (3H, d, $J = 7.1$ Hz), 0.28 (9H, s); ^{13}C NMR (125 MHz, CDCl_3) δ_{C} : 187.3, 136.6, 126.3, 122.1, 120.6, 120.3, 119.3, 119.1, 111.3, 102.2, 98.2, 53.1, 27.3, 21.0, -0.75; HRMS (ESI, +ve) m/z : calcd. for $\text{C}_{25}\text{H}_{20}\text{NO}$: 284.1471, found: 288.1471 $[\text{M} + \text{H}]^+$.

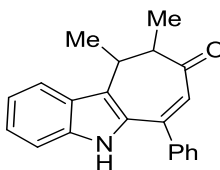
10-Isopropyl-6-phenyl-9,10-dihydrocyclohepta[b]indol-8(5H)-one (205)



Prepared according to general procedure B (reaction time = 8 h, reflux), using indole (31 mg, 0.27 mmol, 1 equiv.), **191** (58 mg, 0.29, 1 equiv.), sodium tetrachloroaurate (III) hydrate (11 mg, 0.03 mmol, 0.1 equiv.), acetonitrile (2 mL). Purification was achieved by flash chromatography to afford **205** as a yellow oil (60 mg, 72 %).

FTIR (thin film) ν_{max} : 3335.4, 3059.2, 2958.1, 1626.1, 1583.9, 1566.8, 1535.0. ^1H NMR (500 MHz, CDCl_3) δ : 7.84 (1H, s), 7.67 (1H, d, $J = 8.1$ Hz), 7.55–7.43 (5H, m), 7.30–7.22 (2H, m), 7.20–7.14 (1H, m), 6.19 (1H, s), 3.21 (1H, dd, $J = 15.2, 5.1$ Hz), 3.12–3.00 (2H, m), 2.22–2.10 (1H, m), 1.12 (3H, d, $J = 6.6$ Hz), 0.91 (3H, d, $J = 6.6$ Hz); ^{13}C NMR (125 MHz) δ : 199.9, 145.6, 139.8, 135.4, 129.9, 129.4, 128.9, 128.7, 128.3, 125.5, 124.5, 120.4, 120.2, 111.3, 45.8, 37.5, 28.8, 22.7, 20.4; HRMS (ESI, +ve) m/z : calcd. for $\text{C}_{22}\text{H}_{22}\text{NO}$: 316.1701, found: 316.1722 $[\text{M} + \text{H}]^+$.

9,10-Dimethyl-6-phenyl-9,10-dihydrocyclohepta[b]indol-8(5H)-one (**206**)

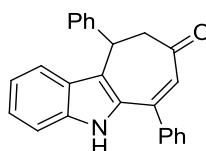


Prepared according to general procedure B (reaction time = 18 h, RT), using indole (69 mg, 0.60 mmol, 1.05 equiv.), **190** (100 mg, 0.54 mmol, 1 equiv.), sodium tetrachloroaurate (III) hydrate (11 mg, 0.03 mmol, 5 mol%), acetonitrile (4 mL). Purification by flash chromatography afforded **206** as a yellow solid (119 mg, 73%).

FTIR (thin film) ν_{max} : 3335, 2057, 2971, 2932, 1634, 1584, 1568, 1538; ^1H NMR (500 MHz, CDCl_3) $\delta_{\text{H (Major)}}$: 7.79 (1H, br. s), 7.67 (1H, app.d., $J = 8.06$ Hz), 7.56–7.42 (5H, m), 7.31–7.24 (2H, m), 7.23–7.15 (1H, m), 6.11 (1H, s), 3.46–3.37 (1H, m), 3.02–2.93 (1H, m), 1.35 (3H, d, $J = 7.5$ Hz), 1.14 (3H, d, $J = 7.5$ Hz); $\delta_{\text{H (Minor)}}$: 7.79 (1H, br. s), 7.67 (1H, app.d., $J = 8.06$ Hz), 7.56–7.42 (5H, m), 7.31–7.24 (2H, m), 7.23–7.15 (1H, m), 6.07 (1H, d, $J = 1.5$ Hz), 3.34–3.23 (1H, m), 3.02–2.93 (1H, m), 1.18 (3H, d, $J = 7.4$ Hz), 1.10 (3H, d, $J = 7.5$ Hz); ^{13}C NMR (125 MHz, CDCl_3) δ : 203.4, 144.3, 139.6, 135.8, 129.7, 129.2, 129.0, 128.5, 128.3, 127.2, 124.7, 123.1, 120.3, 119.4, 111.4, 51.5,

31.6, 18.3, 16.0; HRMS (ESI, +ve) m/z : calcd. for $C_{21}H_{20}NO$: 302.1545, found: 302.1550 $[M + H]^+$.

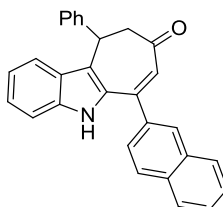
6,10-Diphenyl-9,10-dihydrocyclohepta[b]indol-8(5H)-one (207)



Prepared according to general procedure B (reaction time = 3 h, reflux), using indole (43 mg, 0.42 mmol, 1.05 equiv.), **192** (94 mg, 0.40 mmol, 1 equiv.), sodium tetrachloroaurate (III) hydrate (8 mg, 0.02 mmol, 5 mol%), acetonitrile (2 mL). Purification by flash chromatography afforded **207** as a yellow solid (140 mg, 100%).

MP: 125–126 °C; FTIR (thin film) ν_{\max} : 3057, 2952, 1624, 1536; 1H NMR (500 MHz, $CDCl_3$) δ_H : 7.90 (1H, br. s), 7.53–7.46 (6H, m), 7.32–7.11 (8H, m), 6.12 (1H, d, $J = 1.3$ Hz), 4.86–4.84 (1H, m), 3.52 (1H, dd, $J = 14.9, 6.0$ Hz), 3.43 (1H, dd, $J = 14.9, 3.4$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C : 198.9, 145.0, 139.8, 139.6, 135.6, 131.2, 129.4(x2), 129.0, 128.6(x2), 127.4(x2), 126.8, 124.8, 122.9, 120.7, 119.8, 111.4, 48.7, 35.3; HRMS (ESI, +ve) m/z : calcd. for $C_{25}H_{20}NO$ 350.1544 found 350.1564 $[M + H]^+$.

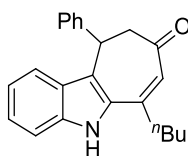
6-(Naphthalen-2-yl)-10-phenyl-9,10-dihydrocyclohepta[b]indol-8(5H)-one (208)



Prepared according to general procedure B (reaction time = 24 h, RT), using indole (22 mg, 0.19 mmol, 1.05 equiv.), **193** (50 mg, 0.18 mmol, 1 equiv.), sodium tetrachloroaurate (III) hydrate (4 mg, 0.01 mmol, 5 mol%), acetonitrile (2 mL). Purification by flash chromatography afforded **208** as a yellow oil (68 mg, 97%).

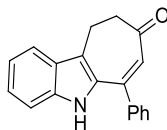
FTIR (thin film) ν_{\max} : 3333, 3058, 2981, 2889, 1626, 1581, 1538; ^1H NMR (400 MHz, CDCl_3) δ_{H} : 8.01–7.90 (5H, m), 7.64–7.58 (2H, m), 7.55 (1H, app.dd., $J = 8.4, 1.7$ Hz) 7.50 (1H, app.dd., $J = 8.4, 0.6$ Hz), 7.33–7.29 (3H, m), 7.27–7.23 (2H, m), 7.21 (1H, tt, $J = 7.0, 1.7$ Hz), 7.15–7.11 (1H, m), 6.23 (1H, d, $J = 1.4$ Hz), 4.88 (1H, dd, $J = 6.0, 3.7$ Hz), 3.55 (1H, ddd, $J = 15.0, 6.0, 1.4$ Hz), 3.47 (1H, dd, $J = 15.0, 3.7$ Hz); ^{13}C NMR (125 MHz, CDCl_3) δ_{C} : 199.0, 145.3, 139.9, 137.0, 135.7, 133.5, 133.1, 129.6, 128.8, 128.7, 128.4, 128.1, 127.9, 127.6, 127.5, 127.2, 127.1, 126.9, 126.1, 124.8, 123.0, 120.7, 119.8, 111.6, 48.8, 35.4; HRMS (ESI, +ve) m/z : calcd. for $\text{C}_{29}\text{H}_{21}\text{NONa}$: 422.1521, found: 422.1524 $[\text{M} + \text{Na}]^+$.

6-Butyl-10-phenyl-9,10-dihydrocyclohepta[b]indol-8(5H)-one (209)



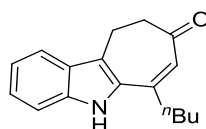
Prepared according to general procedure B (reaction time = 36 h, reflux), using indole (43 mg, 0.42 mmol, 1.05 equiv.), **194** (85 mg, 0.40 mmol, 1 equiv.), sodium tetrachloroaurate (III) hydrate (8 mg, 0.02 mmol, 5 mol%), acetonitrile (2 mL). Purification by flash chromatography afforded **209** as a yellow oil (88 mg, 67%).

FTIR (thin film) ν_{\max} : 3060, 3024, 2956, 2929, 2871, 1715, 1620, 1530; ^1H NMR (400 MHz, CDCl_3) δ_{H} : 8.28 (1H, br. s), 7.45–7.10 (9H, m), 6.05 (1H, s), 4.77–4.72 (1H, m), 3.42 (1H, dd, $J = 14.7, 5.6$ Hz), 3.31 (1H, dd, $J = 14.7, 3.7$ Hz), 2.76–2.56 (2H, m), 1.71–1.37 (4H, m), 0.95 (3H, t, $J = 7.2$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ_{C} : 199.2, 144.9, 139.7, 135.6, 132.0, 128.5, 128.4, 128.2, 127.6, 127.4, 124.7, 122.4, 120.6, 119.7, 111.3, 48.2, 36.3, 35.1, 31.2, 22.3, 12.9; HRMS (ESI, +ve) m/z : calcd. for $\text{C}_{23}\text{H}_{24}\text{NO}$ 330.1858 found 330.1827 $[\text{M} + \text{H}]^+$.

6-Phenyl-9,10-dihydrocyclohepta[b]indol-8(5H)-one (210)

Prepared according to general procedure B (reaction time = 12 h), using indole (43 mg, 0.42 mmol, 1.05 equiv.), **195** (63 mg, 0.40 mmol, 1 equiv.), sodium tetrachloroaurate (III) hydrate (8 mg, 0.02 mmol, 5 mol%), acetonitrile (2 mL). Purification by flash chromatography afforded **210** as a yellow oil (108 mg, 99%).

FTIR (thin film) ν_{max} : 3058, 2927, 1723, 1624, 1538; ^1H NMR (500 MHz, CDCl_3) δ_{H} : 7.78 (1H, br. s), 7.67 (1H, d, $J = 8.3$ Hz), 7.53–7.46 (5H, m), 7.30–7.25 (2H, m), 7.21–7.17 (1H, m), 6.24 (1H, s), 3.23–3.20 (2H, m), 2.97–2.94 (2H, m); ^{13}C NMR (125 MHz, CDCl_3) δ_{C} : 200.6, 145.2, 139.7, 135.7, 131.4, 129.4, 129.0, 128.7, 128.4, 127.0, 124.6, 121.3, 120.4, 119.6, 111.4, 42.5, 18.2; HRMS (ESI, +ve) m/z : calcd. for $\text{C}_{19}\text{H}_{16}\text{NO}$ 274.1232 found 274.1227 $[\text{M} + \text{H}]^+$.

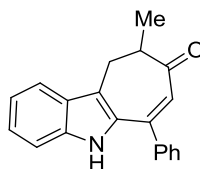
6-Butyl-9,10-dihydrocyclohepta[b]indol-8(5H)-one (211)

Prepared according to general procedure B (reaction time = 96 h, reflux), using indole (43 mg, 0.42 mmol, 1.05 equiv.), **196** (54 mg, 0.4 mmol, 1 equiv.), sodium tetrachloroaurate (III) hydrate (8 mg, 0.02 mmol, 5 mol%), acetonitrile (2 mL). Purification by flash chromatography afforded **211** as a yellow oil (61 mg, 60%).

FTIR (thin film) ν_{max} : 3058, 2955, 2927, 2869, 1718, 1616, 1589, 1574; ^1H NMR (500 MHz, CDCl_3) δ_{H} : 8.16 (1H, br. s), 7.63 (1H, app. d, $J = 7.2$ Hz), 7.40 (1H, app. d, $J = 7.2$ Hz), 7.31–7.28 (1H, m), 7.18 (1H, app. t, $J = 7.2$ Hz), 6.15 (1H, s), 3.08–3.05 (2H, m), 2.85–2.83 (2H, m), 2.64 (2H, app. t, $J = 7.8$ Hz), 1.69–1.62 (2H, m), 1.46 (1H, sext, $J = 7.2$ Hz), 0.98 (3H, t, $J = 7.2$ Hz); ^{13}C NMR (125 MHz, CDCl_3) δ_{C} : 200.8, 145.3,

135.7, 132.2, 127.4, 127.1, 124.4, 120.8, 120.4, 119.5, 111.3, 41.9, 36.3, 31.3, 22.5, 18.1, 13.9; HRMS (ESI, +ve) m/z : calcd. for $C_{17}H_{19}NONa$ 276.1364 found 276.1378 [$M + Na$] $^{+}$.

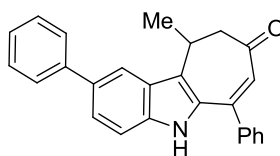
9-Methyl-6-phenyl-9,10-dihydrocyclohepta[b]indol-8(5H)-one (212)



Prepared according to general procedure B (reaction time = 8 h, RT), using indole (36 mg, 0.31 mmol, 1.05 equiv.), **197** (50 mg, 0.29, 1 equiv.), sodium tetrachloroaurate (III) hydrate (6 mg, 0.015 mmol, 5 mol%), acetonitrile (2 mL). Purification by flash chromatography afforded **212** as a yellow oil (64 mg, 76 %).

FTIR (thin film) ν_{\max} : 3324, 2981, 1629, 1540; 1H NMR (300 MHz, $CDCl_3$) δ_H : 7.79 (1H, br. s), 7.58 (1H, app.d., $J = 7.7$ Hz), 7.48–7.28 (5H, m), 7.22–6.98 (3H, m), 6.10 (1H, s), 3.12 (1H, dd, $J = 15.4, 2.0$ Hz), 3.04–2.74 (2H, m), 1.15 (3H, d, $J = 6.7$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C : 201.7, 143.1, 138.5, 134.7, 130.2, 128.3, 127.9, 127.7, 126.9, 126.6, 123.4, 119.3, 118.5, 118.3, 110.4, 43.9, 24.8, 14.8; HRMS (ESI, +ve) m/z : calcd. for $C_{20}H_{18}NO$: 288.1388, found: 288.1405 [$M + H$] $^{+}$.

10-Methyl-2,6-diphenyl-9,10-dihydrocyclohepta[b]indol-8(5H)-one¹³⁸ (214)



To a microwave vial was added **166** (62 mg, 0.15 mmol, 1 equiv.), phenylboronic acid (18 mg, 0.15 mmol, 1 equiv.), K_2CO_3 (31 mg, 0.23 mmol, 1.5 equiv.) and $Pd(PPh_3)_4$ (7 mg, 0.006 mmol, 4 mol%). Acetonitrile (3 mL) and water (1 mL) were added and the vessel was sealed, followed by sonication and purging with nitrogen concurrently for 10

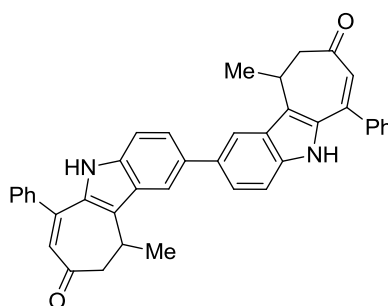
minutes. The reaction mixture was then subjected to microwave irradiation at 120 °C for 30 minutes. The reaction mixture was then passed through a plug of silica gel before concentration *in vacuo*. Purification was achieved by flash chromatography, eluting with 8:1 Pet/EtOAc, affording **214** as a yellow oil (50 mg, 92%).

FTIR (thin film) ν_{\max} : 3317, 2956, 2922, 2854; ^1H NMR (500 MHz, CDCl_3) δ_{H} : 7.87 (1H, s), 7.82 (1H, br. s), 7.69–7.65 (2H, m), 7.55–7.45 (8H, m), 7.39–7.32 (2H, m), 6.21 (1H, d, $J = 1.3$ Hz), 3.77–3.66 (1H, m), 3.21 (1H, dd, $J = 14.6, 3.3$ Hz), 2.98 (1H, dd, $J = 14.6, 1.3$ Hz), 1.39 (1H, d, $J = 7.5$ Hz); ^{13}C NMR (125 MHz, CDCl_3) δ_{C} : 199.8, 145.0, 142.0, 139.7, 138.2, 135.0, 134.1, 130.6, 129.3, 129.0, 128.8, 128.5, 127.3, 126.8, 126.4, 124.7, 117.7, 111.7, 48.2, 25.0, 17.1; HRMS (ESI, +ve) m/z : calcd. for $\text{C}_{26}\text{H}_{21}\text{NONa}$: 386.1521, found: 386.1526 $[\text{M} + \text{Na}]^+$.

To a microwave vial was added **165** (62mg, 0.15 mmol, 1 equiv.), iodobenzene (17 μL , 0.15 mmol, 1 equiv.), K_2CO_3 (31 mg, 0.225 mmol, 1.5 equiv.) and $\text{Pd}(\text{PPh}_3)_4$ (7 mg, 0.006 mmol, 4 mol%). Acetonitrile (3 mL) and water (1 mL) were added and the vessel was sealed, followed by sonication and purging with nitrogen concurrently for 10 minutes. The reaction mixture was then subjected to microwave irradiation at 120 °C for 30 minutes. The reaction mixture was then passed through a plug of silica gel before concentration *in vacuo*. Purification was achieved by flash chromatography (8:1 Pet/EtOAc) affording **214** as a yellow oil (54 mg, 99%).

All data as previously stated.

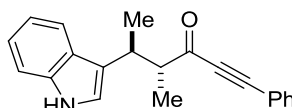
10,10'-Dimethyl-6,6'-diphenyl-9,9',10,10'-tetrahydro-[2,2'-bi(cyclohepta[b]indole)]-8,8'(5H,5'H)-dione¹³⁸ (216)



To a microwave vial was added **165** (62mg, 0.15 mmol, 1 equiv.), **166** (62 mg, 0.15 mmol, 1 equiv.), K₂CO₃ (31 mg, 0.225 mmol, 1.5 equiv.) and Pd(PPh₃)₄ (7 mg, 0.006 mmol, 4 mol%). Acetonitrile (3 mL) and water (1 mL) were added and the vessel was sealed, followed by sonication and purging with nitrogen concurrently for 10 minutes. The reaction mixture was then subjected to microwave irradiation at 120 °C for 30 minutes. The reaction mixture was then passed through a plug of silica gel before concentration *in vacuo*. Purification was achieved by flash chromatography, eluting with 8:1 Pet/EtOAc, affording **216** as a yellow oil (75 mg, 87%).

FTIR (thin film) ν_{max} : 3353, 2960, 1630, 1583, 1565, 1531; ¹H NMR (500 MHz, CDCl₃) δ_{H} : 7.93–7.87 (2H, m), 7.79 (2H, s), 7.63–7.57 (10H, m), 7.36 (2H, app.d., J = 8.5 Hz), 6.22 (2H, d = 1.5 Hz), 3.80 (2H, m), 3.23 (2H, dt, J = 14.5, 2.9 Hz), 3.00 (2H, ddd, J = 14.5, 6.5, 1.1 Hz), 1.41 (3H, d, J = 7.3 Hz), 1.40 (3H, d, J = 7.3 Hz); ¹³C NMR (125 MHz, CDCl₃) δ_{C} : 199.8, 145.0, 139.7, 134.9, 134.8, 130.6, 129.3, 129.0(x2), 128.5, 127.4, 126.4, 125.1, 117.6, 111.7, 48.2, 25.0, 17.1; HRMS (ESI, +ve) m/z : calcd. for C₄₀H₃₃N₂O₂: 573.2542, found: 573.2535 [M + H]⁺.

5-(1H-Indol-3-yl)-4-methyl-1-phenylhex-1-yn-3-one¹²³ (**218**)

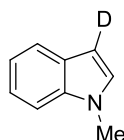


To indole (27 mg, 0.23 mmol, 1 equiv.) in a round bottomed flask, was added a solution of **190** (42 mg, 0.23 mmol, 1 equiv.) in acetonitrile (1 mL) at 0 °C. A solution of 2,4-dinitrobenzenesulfonic acid (3 mg, 0.01 mmol, 5 mol%) in acetonitrile (1 mL) was added and stirred at room temperature for 2 hours. The solution was filtered through celtie and concentrated in vacuo. 2:1 dr as determined by ¹H NMR analysis of crude reaction mixture.

¹H NMR (500 MHz, CDCl₃) δ_{H} (Major): 8.06 (1H, br. s), 7.71 (1H, app. d, J = 7.9 Hz), 7.61–7.54 (2H, m), 7.55–7.38 (4H, m), 7.29–7.15 (2H, m), 7.11–7.08 (1H, m), 3.59–3.49 (1H, m), 3.21–3.11 (1H, m), 1.51 (3H, d, J = 7.0 Hz), 1.20 (3H, d, J = 6.9 Hz); δ_{H} (Minor): 8.06 (1H, br. s), 7.82 (1H, app. d, J = 7.9 Hz), 7.61–7.54 (2H, m), 7.55–7.38 (4H,

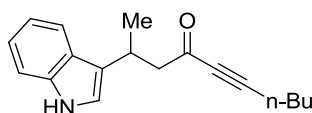
m), 7.29–7.15 (2H, m), 7.11–7.08 (1H, m), 4.02–3.93 (1H, m), 3.32–3.23 (1H, m), 1.40 (3H, d, $J = 7.0$ Hz), 1.21 (3H, d, $J = 6.8$ Hz).

3-Deutero-1-methylindole¹³⁹ (C-3-²H-168)



A flask was charged with freshly distilled 1-methylindole (1.56 mL, 13.2 mmol) and then flushed with argon. To this was added D₂O (4 mL), and the mixture heated to 105 °C overnight with very vigorous stirring. Upon cooling, the solution was extracted with hexanes (3 × 5 mL), and dried over Na₂SO₄. The solvent was removed and the final product was purified by distillation from molecular sieves. The product was 94 % enriched with deuterium in the 3-position, as determined by ¹H NMR. (See appendix 6.3.1)

2-(1H-Indol-3-yl)dec-5-yn-4-one¹²³ (219)

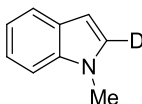


To a solution of **187** (280 mg, 1.90 mmol, 1 equiv.) in acetonitrile (10 mL) at 0 °C was added DNsOH (23 mg, 0.10 mmol, 5 mol%) portionwise, the reaction was then allowed to stir for 40 minutes. Upon completion, the reaction was filtered through K₂CO₃ and concentrated *in vacuo*. Purification was achieved by flash chromatography, eluting with 8:1 Pet/EtOAc, to provide **219** as a yellow oil (404 mg, 81%).

FTIR (thin film) ν_{\max} : 3414, 2959, 2933, 2872, 2208, 1659; ¹H NMR (500 MHz, CDCl₃) δ_{H} : 8.03 (1H, br. s), 7.68 (1H, app. d, $J = 8.0$ Hz), 7.36 (1H, app. d, $J = 8.0$ Hz), 7.21 (1 H, app. t, $J = 7.5$ Hz), 7.14 (1H, app. t, $J = 7.5$ Hz), 6.98 (1H, d, $J = 1.6$ Hz), 3.85–3.72 (1H, m), 3.08 (1H, dd, $J = 15.7, 5.8$ Hz), 2.81 (1H, dd, $J = 15.7, 8.7$

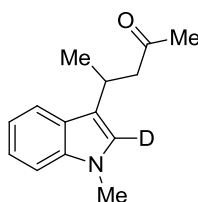
Hz), 2.35 (2H, t, $J = 6.8$ Hz), 1.61–1.49 (2H, m), 1.48–1.37 (5H, m), 0.93 (3H, t, $J = 7.4$ Hz); ^{13}C NMR (125 MHz, CDCl_3) δ_{C} : 187.9, 136.6, 126.4, 122.1, 120.7, 120.3, 119.3, 119.1, 111.4, 94.9, 81.1, 53.2, 29.7, 27.4, 22.0, 21.0, 18.7, 13.5; HRMS (ESI, +ve) m/z : calcd. for $\text{C}_{18}\text{H}_{22}\text{NO}$: 268.1701, found: 268.1683 $[\text{M} + \text{H}]^+$.

2-Deutero-1-methylindole¹³⁹ (C-2-²H-168)



A flame dried flask was charged with freshly distilled 1-methylindole (1.56 mL, 13.2 mmol) and purged with nitrogen. Anhydrous THF (20 mL) was added and the solution cooled to 0 °C. *n*-BuLi (1.6 M in hexanes, 14.9 mL, 23.8 mmol) was added drop wise, and the resulting solution warmed to rt and stirred for an additional 20 minutes. Very slowly, D_2O (1 mL) was added drop wise. After the solution was fully quenched, it was extracted with hexanes (3×5 mL). The organic solution was dried over Na_2SO_4 and concentrated *in vacuo*. The final product was purified by distillation from molecular sieves. The product was 98 % enriched with deuterium in the 2-position, as determined by ^1H NMR (See appendix 6.3.2).

4-(2-Deutero-indol-3-yl)pentan-2-one (222)

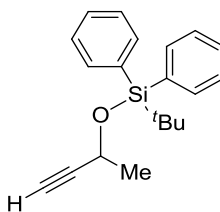


To a solution of **C-3-²H-168** (65 μL , 0.51 mmol, 1 equiv.) in MeCN (1 mL) was added 3-penten-2-one (50 μL , 0.51 mmol, 1 equiv.). A solution of AuCl_3 (8 mg, 5 mol%) in MeCN (1 mL) was added and the reaction allowed to stir for 40 mins. The reaction mixture was then filtered through a pad of celite and concentrated *in vacuo*. The crude residue was subjected to flash chromatography, eluting with 8:1 Pet/EtOAc, affording **221** as a light yellow oil (76 mg, 69%). The product was 72 % enriched with deuterium in the 2-position, as determined by ^1H NMR (See appendix 6.3.3)

FTIR (thin film) ν_{\max} : 2060, 2927, 2882, 1709; ^1H NMR (300 MHz, CD_3CN) δ_{H} : 7.67–7.61 (1H, m), 7.38–7.33 (1H, m), 7.24–7.17 (1H, m), 7.11–7.04 (1H, m), 6.97 (1H, s, 70% D incorporation), 3.74 (3H, s), 3.63–3.51 (1H, m), 2.92 (1H, dd, $J = 16.5, 7.0$ Hz), 2.73 (1H, dd, $J = 16.5, 7.0$ Hz), 2.08 (3H, s), 1.33 (3H, d, $J = 7.0$ Hz); ^{13}C NMR (75 MHz, CD_3CN) δ_{C} : 207.6, 136.9, 126.4, 124.9, 121.0, 120.9, 118.7, 118.1, 109.1, 50.5, 31.6, 29.1, 26.2, 20.7; HRMS (ESI, +ve) m/z : calcd. for $\text{C}_{14}\text{H}_{16}\text{DNONa}$, 239.1271 found 239.1273 $[\text{M} + \text{Na}]^+$.

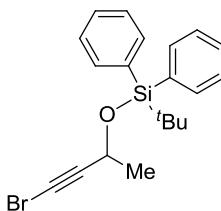
5.3 Chapter 3

(But-3-yn-2-yloxy)(*tert*-butyl)diphenylsilane¹³⁷ (**271**)



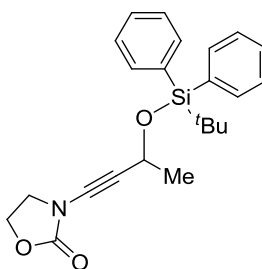
To a solution of 3-butyn-2-ol (900 μL , 11.4 mmol, 1 equiv.) in THF (35 mL) was added triethylamine (3.30 mL, 22.7 mmol, 2 equiv.), TBDPSCl (3.20 mL, 12.5 mmol, 1.1 equiv.) and DMAP (140 mg, 1.14 mmol, 10 mol%). The resultant mixture was stirred at rt for 18 h, diluted with hexane (150 mL) and washed with NH_4Cl (sat) (150 mL) and brine (150 mL) and dried over MgSO_4 , filtered and concentrated *in vacuo*. Purification via flash chromatography, eluting with 100 % Pet, afforded **271** as a clear oil (3.27 g, 94 %).

FTIR (thin film) ν_{\max} : 3306, 3072, 3050, 2983, 2960, 2932, 2891, 2858; ^1H NMR (250 MHz, CDCl_3) δ_{H} : 7.71–7.57 (4H, m), 7.40–7.24 (6H, m), 4.38 (1H, dq, $J = 6.5, 2.1$ Hz), 2.25 (1H, d, $J = 2.1$ Hz), 1.31 (3H, d, $J = 6.5$ Hz), 1.00 (9H, s); ^{13}C NMR (75 MHz, CDCl_3) δ_{C} : 136.4, 136.2, 134.1, 133.8, 130.2, 130.1, 128.0, 127.9, 86.5, 71.0, 31.3, 27.3, 25.6, 19.6; MS (ESI:+ve) m/z : calcd for $\text{C}_{20}\text{H}_{24}\text{NaOSi}$: 331.1294, found: 331.1496 $[\text{M} + \text{Na}]^+$.

(4-Bromobut-3-yn-2-yloxy)(*tert*-butyl)diphenylsilane¹⁵⁵ (272)

To a solution of the silyl ether **271** (10.0 g, 33.0 mmol, 1 equiv.) in acetone (180 mL) was added *N*-bromosuccinimide (6.46 g, 36.3 mmol, 1.1 equiv.) and AgNO₃ (560 mg, 3.30 mmol, 10 mol%). The resultant mixture was stirred at rt for 3 h, diluted with CHCl₃ (180 mL), filtered through a pad of celite and concentrated *in vacuo*. Purification via flash chromatography, eluting with 100 % Pet, afforded the title product (11.25 g, 88 %) as a light yellow oil.

FTIR (film/cm⁻¹) ν_{max} : 3076, 2985, 2964, 2932, 2894, 2864; ¹H NMR (250 MHz, CDCl₃) δ_{H} : 7.68–7.56 (4H, m), 7.39–7.25 (6H, m), 4.37 (1H, q, *J* = 6.5 Hz), 1.31 (3H, d, *J* = 6.5 Hz) 0.99 (9H, s); ¹³C NMR (75 MHz, CDCl₃) δ_{C} : 136.3, 136.2, 134.0, 133.8, 130.2, 130.1, 128.0, 127.9, 82.7, 61.2, 44.3, 27.2, 25.4, 19.6; MS (ESI:+ve) *m/z*: calcd for C₂₀H₂₃NaOSiBr: 409.0599, found: 409.0580 [M + Na⁺].

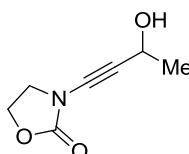
3-(3-(*tert*-Butyldiphenylsilyloxy)but-1-ynyl)oxazolidin-2-one¹⁵⁶ (274)

To a solution of **272** (1.50 g, 3.80 mmol, 1.1 equiv.) and oxazolidinone (300 mg, 3.50 mmol, 1 equiv.) in toluene (50 mL) was added CuSO₄·5H₂O (175 mg, 0.70 mmol, 20 mol%), 1,10-phenanthroline (250 mg, 1.40 mmol, 40 mol%) and K₃PO₄ (1.50 g, 7.00 mmol, 2 equiv.). The suspension was then refluxed for 48 h, filtered through celite and concentrated *in vacuo*. Purification via flash chromatography, eluting with 4:1

Pet/EtOAc, afforded ynamide **274** as a white powder (0.88g, 64%). Recrystallisation (Pet/DCM) afforded the title compound as colourless crystals.

MP: 110–112; FTIR (film/cm⁻¹) ν_{\max} : 2929, 2856, 2262, 1777; ¹H NMR (250 MHz, CDCl₃) δ_{H} : 7.71–7.59 (4H, m), 7.36–7.26 (6H, m), 4.58 (1H, q, J = 6.5), 4.25 (2H, t, J = 8.0 Hz), 3.51 (2H, m), 1.37 (3H, d, J = 6.5 Hz), 0.99 (9H, s); ¹³C NMR (75 MHz, CDCl₃) δ_{C} : 156.2, 136.4, 136.2, 134.3, 134.1, 130.1, 129.9, 128.0, 127.8, 74.6, 73.9, 63.2, 60.5, 47.0, 27.3, 25.5, 19.5; MS (ESI:+ve) m/z : calcd for C₂₃H₂₈NO₃Si: 394.1838, found: 394.1822 [M + H⁺]

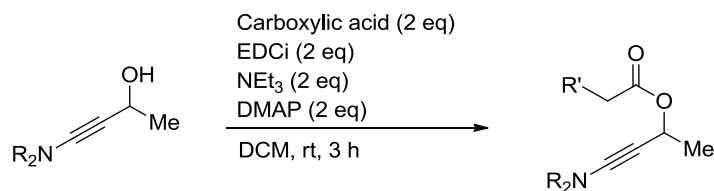
3-(3-Hydroxybut-1-ynyl)oxazolidin-2-one¹⁵⁵ (**266**)



To a solution of the protected ynamide **274** (3.00g, 7.60 mmol, 1 equiv.) in THF (175 mL) was added TBAF (1M in THF, 15.2 mL, 15.2 mmol, 2 equiv.) at 0 °C. The resultant solution was then warmed to rt, after 40 min the reaction mixture was hydrolysed with NH₄Cl (sat) (25 mL) and extracted with EtOAc (3 × 25 mL). The combined extracts were dried over MgSO₄, filtered and concentrated *in vacuo*. The crude material was purified by rapid filtration through silica gel, eluting with 100% EtOAc, to give alcohol **266** as a clear oil (1.03 g, 87%).

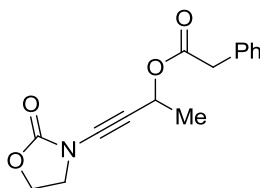
FTIR (film/cm⁻¹) ν_{\max} : 3245, 2924, 2854, 1765; ¹H NMR (250 MHz, CDCl₃) δ_{H} : 4.68 (1H, q, J = 6.6 Hz), 4.48–4.26 (2H, m), 3.94–3.87 (2H, m), 2.49 (1H, br s), 1.47 (3H, d, J = 6.6Hz); ¹³C NMR (75 MHz, CDCl₃) δ_{C} : 156.3, 74.1, 73.4, 63.1, 58.3, 46.8, 24.2; MS (ESI:+ve) m/z : calcd for C₇H₉NNaO₃: 178.0480, found: 178.0476 [M + Na⁺].

5.3.1 General procedure C for the preparation of ynamides esters¹⁵⁷



To a solution of EDCi (2 equiv.) in DCM was successively added triethylamine (2 equiv.), DMAP (20 mol%), phenylacetic acid (2 equiv.) and propargylic alcohol (1 equiv.). After 3 hours at room temperature the resultant solution was washed with 10% citric acid (3 x 10 ml), NaHCO₃ (sat) (3 x 10 ml) and brine (10 ml). The organic extract was then dried over MgSO₄ and concentrated *in vacuo*. The crude mixture was then subjected to column chromatography for purification, eluting with 4:1 Pet/EtOAc.

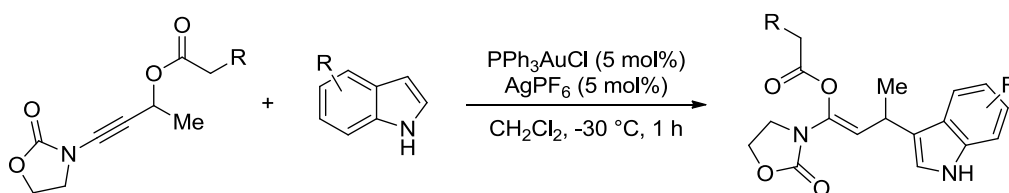
4-(2-Oxooxazolidin-3-yl)but-3-yn-2-yl 2-phenylacetate (**264**)



Prepared according to general procedure C using; propargyl alcohol **266** (290 mg, 1.89 mmol, 1 equiv.), phenylacetic acid (510 mg, 3.78 mmol, 2 equiv.), EDCi (720 mg, 3.78 mmol, 2 equiv.), triethylamine (550 μ L, 3.78 mmol, 2 equiv.), DMAP (50 mg, 0.76 mmol, 20 mol%) and DCM (30 mL). Purification was achieved by recrystallization from DCM/hexane to afford **264** as colourless crystals (0.45 g, 88 %).

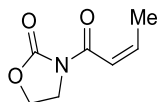
MP: 115–116; FTIR (film/cm⁻¹) ν_{max} : 3031, 2991, 2915, 2262, 1760, 1733; ¹H NMR (250 MHz, CDCl₃) δ_{H} : 7.40–7.30 (5H, m), 5.64 (1H, q, J = 6.8 Hz) 4.46 (2H, m), 3.92 (2H, m), 3.66 (2H, s), 1.55 (3H, d, J = 6.8 Hz); ¹³C NMR (75 MHz, CDCl₃) δ_{C} : 170.5, 155.9, 133.7, 129.3, 128.6, 127.1, 75.1, 70.1, 63.1, 61.0, 46.7, 41.2, 21.3; MS (ESI:+ve) m/z : calcd for C₁₅H₁₅NNaO₄ : 296.0899, found: 296.0899 [M + Na]⁺.

5.3.2 General procedure D for the [3,3]-rearrangement and nucleophilic addition of ynamido esters



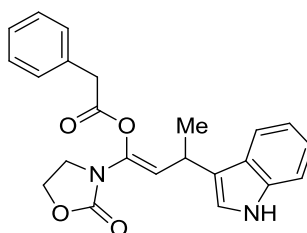
To a solution of indole (1 equiv.) and ynamido ester (1 equiv.) in DCM at -30 °C was added PPh_3AuCl (5 mol%) and AgPF_6 (5mol%) portion-wise over 45 mins. Upon consumption of starting material, the reaction was filtered through a pad of silica and concentrated *in vacuo*. Purification was achieved by flash chromatography, eluting with 2:1 Pet/EtOAc.

(Z)-3-(But-2-enoyl)oxazolidin-2-one (**275**)



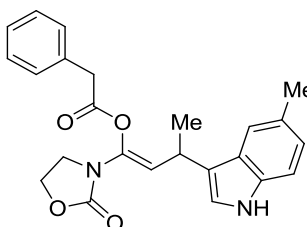
To a solution of **264** (50 mg, 0.18 mmol, 1 equiv.) in DCM (2 mL) was added $\text{AuCl}(\text{PPh}_3)$ (4.5 mg, 0.01 mmol, 5 mol%) and AgSbF_6 (3.4 mg, 0.01 mmol, 5 mol%). The reaction mixture was allowed to stir at room temperature for 5 minutes before being filtered through a pad of silica. Purification by flash chromatography afforded **275** as a light yellow oil (1 mg, 4%).

FTIR (film/ cm^{-1}) ν_{max} : 2981, 2920, 1770, 1679, 1628; ^1H NMR (500 MHz, CDCl_3) δ_{H} : 7.03 (1H, dq, $J = 11.7, 1.8$ Hz), 6.49 (1H, dq, $J = 11.7, 7.3$ Hz), 4.42 (2H, app. t, $J = 8.0$ Hz), 4.07 (2H, app. t, $J = 8.0$ Hz), 2.16 (3H, dd, $J = 7.3, 1.8$ Hz); ^{13}C NMR (75 MHz, CDCl_3) δ_{C} : 165.2, 153.5, 146.8, 119.7, 62.0, 42.5, 16.2; MS (ESI:+ve) m/z : calcd for $\text{C}_7\text{H}_9\text{NO}_3\text{Na}$: 178.0480, found: 178.0495, $[\text{M} + \text{Na}]^+$.

(Z)-3-(1H-Indol-3-yl)-1-(2-oxooxazolidin-3-yl)but-1-en-1-yl 2-phenylacetate (279)

Prepared according to general procedure D using, indole (21 mg, 0.18 mmol, 1 equiv.), **264** (50 mg, 0.18 mmol, 1 equiv.), AuCl(PPh₃) (4.5 mg, 0.01 mmol, 5 mol%), AgPF₆ (2.3 mg, 0.01 mmol, 5 mol%) and DCM (2 mL). Purification by flash chromatography afforded enamide **279** as a light yellow oil (65 mg, 93%).

FTIR (thin film) ν_{max} : 3659, 3408, 2981, 2972, 2889, 1758, 1686, 1621; ¹H NMR (500 MHz, CDCl₃) δ_{H} : 8.06 (1H, br.s), 7.55 (1H, d, $J = 7.8$ Hz), 7.35–7.32 (5H, m), 7.19 (1H, app.t, $J = 7.8$ Hz), 7.10 (1H, app.t, $J = 7.8$ Hz), 6.93 (1H, d, $J = 2.3$ Hz), 5.23 (1H, d, $J = 9.6$ Hz), 4.26 (2H, app.t, $J = 8.1$ Hz), 3.80 (2H, s), 3.77–3.71 (1H, m), 3.69–3.63 (2H, m), 1.42 (3H, d, $J = 6.8$ Hz); ¹³C NMR (125 MHz, CDCl₃) δ_{C} : 169.4, 154.4, 136.5, 136.3, 133.0, 129.5, 128.8, 127.5, 126.5, 122.0, 120.4, 119.7, 119.3, 119.3, 114.6, 111.2, 61.7, 45.3, 40.7, 27.7, 20.8; HRMS (ESI, +ve) m/z : calcd. for C₂₃H₂₂N₂O₄Na: 413.1483, found: 413.1477 [M + Na]⁺.

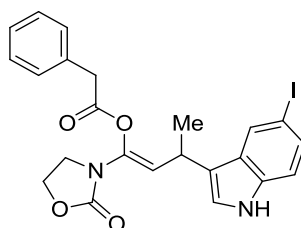
(Z)-3-(5-Methyl-1H-indol-3-yl)-1-(2-oxooxazolidin-3-yl)but-1-en-1-yl 2-phenylacetate (280)

Prepared according to general procedure D using, 5-methyl indole (24 mg, 0.18 mmol, 1 equiv.), **264** (50 mg, 0.18 mmol, 1 equiv.), AuCl(PPh₃) (4.5 mg, 0.01 mmol, 5 mol%),

AgPF₆ (2.3 mg, 0.01 mmol, 5 mol%) and DCM (2 mL). Purification by flash chromatography afforded enamide **280** as a light yellow oil (65 mg, 89%).

FTIR (thin film) ν_{\max} : 3659, 3407, 2981, 2972, 2889, 1755, 1689, 1627; ¹H NMR (400 MHz, CDCl₃) δ_{H} : 7.95 (1H, br.s), 7.63–7.50 (1H, m), 7.40–7.32 (5H, m), 7.27 (1H, d, J = 8.3 Hz), 7.06 (1H, dd, J = 8.3, 1.6 Hz), 6.93 (1H, dd, J = 2.6, 0.7 Hz), 5.29 (1H, d, J = 9.6 Hz), 4.31 (2H, app.t, J = 8.1 Hz), 3.86 (2H, s), 3.79–3.66 (3H, m), 2.51 (3H, s), 1.44 (3H, d, J = 6.9 Hz); ¹³C NMR (100 MHz, CDCl₃) δ_{C} : 169.4, 154.5, 136.3, 134.9, 133.1, 129.5, 128.8, 128.4, 127.5, 126.7, 123.6, 120.5, 119.2, 119.0, 114.9, 110.9, 61.7, 45.4, 40.7, 27.7, 21.6, 21.0; HRMS (ESI, +ve) m/z : calcd. for C₂₄H₂₄N₂O₄Na: 427.1634, found: 427.1615 [M + Na]⁺.

(Z)-3-(5-Iodo-1H-indol-3-yl)-1-(2-oxooxazolidin-3-yl)but-1-en-1-yl 2-phenylacetate (281)

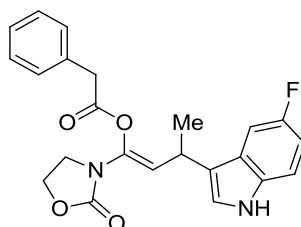


Prepared according to general procedure D using, 5-iodoindole (45 mg, 0.18 mmol, 1 equiv.), **264** (50 mg, 0.18 mmol, 1 equiv.), AuCl(PPh₃) (4.5 mg, 0.01 mmol, 5 mol%), AgPF₆ (2.3 mg, 0.01 mmol, 5 mol%) and DCM (2 mL). Purification by flash chromatography afforded enamide **281** as a orange solid (87 mg, 92%). Recrystallisation (Pet/DCM) afforded the title compound as orange crystals.

MP: 135–136 °C; FTIR (thin film) ν_{\max} : 3261, 2970, 2911, 1772, 1720, 1683; ¹H NMR (400 MHz, CDCl₃) δ_{H} : 8.15 (1H, br. s), 7.91–7.87 (1H, m), 7.46 (1H, dd, J = 8.5, 1.7 Hz), 7.42–7.33 (5H, m), 7.15 (1H, d, J = 8.5 Hz), 6.94–6.91 (1H, m), 5.32 (1H, d, J = 9.7 Hz), 4.36–4.30 (2H, m), 3.84 (2H, s), 3.75–3.69 (2H, m), 3.68–3.57 (1H, m), 1.38 (3H, d, J = 7.0 Hz); ¹³C NMR (100 MHz, CDCl₃) δ_{C} : 169.3, 154.7, 136.3, 135.6, 133.0, 130.3, 129.4, 129.1, 128.9, 128.1, 127.7, 121.3, 119.2, 114.6, 113.3, 82.8, 61.8, 45.2,

40.9, 27.5, 21.2; HRMS (ESI, +ve) m/z : calcd. for $C_{23}H_{21}N_2O_4INa$: 539.0444, found: 539.0472 $[M + Na]^+$.

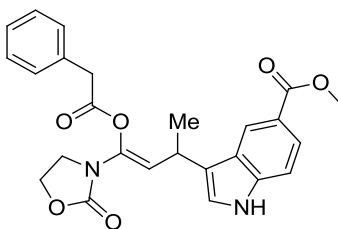
(Z)-3-(5-Fluoro-1H-indol-3-yl)-1-(2-oxooxazolidin-3-yl)but-1-en-1-yl 2-phenylacetate (282)



Prepared according to general procedure D using, 5-fluoroindole (25 mg, 0.18 mmol, 1 equiv.), **264** (50 mg, 0.18 mmol, 1 equiv.), $AuCl(PPh_3)$ (4.5 mg, 0.01 mmol, 5 mol%), $AgPF_6$ (2.3 mg, 0.01 mmol, 5 mol%) and DCM (2 mL). Purification by flash chromatography afforded enamide **282** as a pink oil (74 mg, 99%).

FTIR (thin film) ν_{max} : 3359, 2959, 2924, 1754, 1697; 1H NMR (400 MHz, $(CD_3)_2CO$) δ_H : 10.07 (1H, br. s), 7.43–7.39 (2H, m), 7.38–7.32 (3H, m), 7.32–7.22 (2H, m), 7.21–7.18 (1H, m), 6.89 (1H, td, $J = 9.2, 2.6$ Hz), 5.29 (1H, d, $J = 9.9$ Hz), 4.39–4.32 (2H, m), 3.94 (2H, s), 3.88–3.76 (2H, m), 3.75–3.66 (1H, m), 1.37 (3H, d, $J = 7.0$ Hz); ^{13}C NMR (100 MHz, $(CD_3)_2CO$) δ_C : 168.9, 157.3 (d, $J = 231.6$ Hz), 154.0, 136.9, 133.9, 133.6, 129.6, 128.5, 127.2, 127.0 (d, $J = 8.8$ Hz), 122.9, 119.4 (d, $J = 4.6$ Hz), 112.4, 112.1 (d, $J = 8.8$ Hz), 109.3 (d, $J = 24.6$ Hz), 103.8 (d, $J = 24.6$ Hz), 61.7, 45.0, 40.1, 27.4, 20.5; HRMS (ESI, +ve) m/z : calcd. for $C_{23}H_{21}N_2O_4FNa$: 431.1383, found: 431.1399 $[M + Na]^+$.

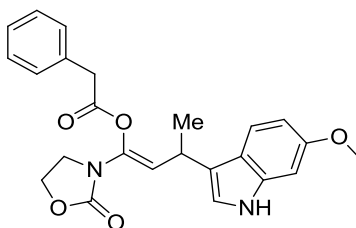
(Z)-Methyl 3-(4-(2-oxooxazolidin-3-yl)-4-(2-phenylacetoxy)but-3-en-2-yl)-1H-indole-5-carboxylate (283)



Prepared according to general procedure D using, indole (32 mg, 0.18 mmol, 1 equiv.), **264** (50 mg, 0.18 mmol, 1 equiv.), AuCl(PPh₃) (4.5 mg, 0.01 mmol, 5 mol%), AgPF₆ (2.3 mg, 0.01 mmol, 5 mol%) and DCM (2 mL). Purification by flash chromatography afforded enamide **283** as an orange oil (43 mg, 53%).

FTIR (thin film) ν_{max} : 3383, 2957, 2923, 2854, 1760, 1703, 1617; ¹H NMR (400 MHz, CDCl₃) δ_{H} : 8.46 (1H, br. s), 8.42–8.39 (1H, m), 7.92 (1H, dd, $J = 7.0, 1.5$ Hz), 7.38–7.29 (6H, m), 7.02–7.00 (1H, m), 5.39 (1H, d, $J = 9.7$ Hz), 4.34–4.28 (2H, m), 4.00 (3H, s), 3.84 (2H, s), 3.80–3.67 (3H, m), 1.43 (1H, d, $J = 7.0$ Hz); ¹³C NMR (100 MHz, CDCl₃) δ_{C} : 169.3, 168.3, 154.7, 139.2, 136.3, 133.0, 129.4, 128.8, 127.6, 126.0, 123.3, 122.4, 121.9, 121.3, 121.1, 114.7, 111.0, 61.8, 51.9, 45.2, 40.8, 27.9, 21.4; HRMS (ESI, +ve) m/z : calcd. for C₂₅H₂₅N₂O₆: 449.1713, found: 449.1749 [M + H]⁺.

(Z)-3-(6-Methoxy-1H-indol-3-yl)-1-(2-oxooxazolidin-3-yl)but-1-en-1-yl 2-phenylacetate (284)

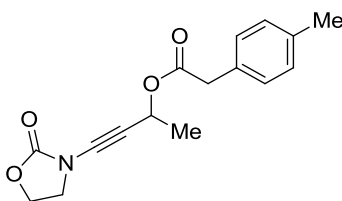


Prepared according to general procedure D using, 6-methoxy indole (27 mg, 0.18 mmol, 1 equiv.), **264** (50 mg, 0.18 mmol, 1 equiv.), AuCl(PPh₃) (4.5 mg, 0.01 mmol, 5 mol%),

AgPF₆ (2.3 mg, 0.01 mmol, 5 mol%) and DCM (2 mL). Purification by flash chromatography afforded enamide **284** as a light brown oil (70 mg, 92%).

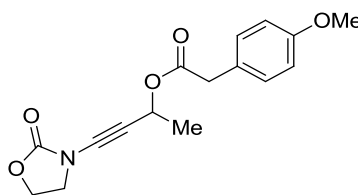
FTIR (thin film) ν_{max} : 3401, 2981, 1754, 1684, 1628, 1628; ¹H NMR (400 MHz, CDCl₃) δ_{H} : 7.96 (1H, s), 7.40 (1H, d, J = 8.6 Hz), 7.39–7.32 (5H, m), 6.88–6.84 (2H, m), 6.80 (1H, dd, J = 8.6, 2.2 Hz), 5.23 (1H, d, J = 9.6 Hz), 3.88 (3H, s), 3.86 (2H, s), 3.74–3.66 (3H, m), 1.43 (3H, d, J = 7.0 Hz); ¹³C NMR (100 MHz, CDCl₃) δ_{C} : 169.4, 156.5, 154.5, 137.3, 136.3, 133.1, 129.5, 128.8, 127.5, 121.0, 120.0, 119.7, 119.1, 114.7, 109.3, 94.7, 61.7, 55.7, 45.4, 40.7, 27.7, 20.8; HRMS (ESI, +ve) m/z : calcd. for C₂₄H₂₄N₂O₅Na: 443.1583, found: 443.1575 [M + Na]⁺.

4-(2-Oxooxazolidin-3-yl)but-3-yn-2-yl 2-(p-tolyl)acetate (**288**)



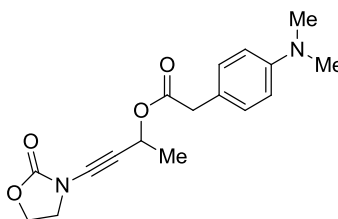
Prepared according to general procedure C using; propargyl alcohol **266** (331 mg, 2.14 mmol, 1 equiv.), 2-(*p*-tolyl)acetic acid (643 mg, 4.28 mmol, 2 equiv.), EDCi (821 mg, 4.28 mmol, 2 equiv.), NEt₃ (591 μ L, 4.28 mmol, 2 equiv.), DMAP (53 mg, 0.43 mmol, 20 mol%) and DCM (40 mL). Purification was achieved by flash chromatography affording ester **288** as an orange solid (0.64 g, 99%). Recrystallisation (Pet/DCM) afforded the title compound as yellow crystals.

MP: 103–105 °C; FTIR (film/cm⁻¹) ν_{max} : 2986, 2264, 1768, 1735, 1520; ¹H NMR (300 MHz, CDCl₃) δ_{H} : 7.20 – 7.17 (2H, m), 7.16 – 7.13 (2H, m), 5.62 (1H, q, J = 6.7 Hz), 4.46 – 4.41 (2H, m), 3.93 – 3.88 (2H, m), 3.60 (2H, s), 2.35 (3H, s), 1.53 (3H, d, J = 6.7 Hz); ¹³C NMR (75 MHz, CDCl₃) δ_{C} : 171.1, 155.9, 137.1, 130.7, 129.2, 129.1, 77.2, 70.2, 63.0, 61.0, 46.7, 40.8, 21.3, 21.1; MS (ESI:+ve) m/z : calcd for C₁₆H₁₇NO₄Na: 310.1055, found: 310.1039 [M + Na]⁺

4-(2-Oxooxazolidin-3-yl)but-3-yn-2-yl 2-(4-methoxyphenyl)acetate (289)

Prepared according to general procedure C using; propargyl alcohol **266** (343 mg, 1.89 mmol, 1 equiv.), 2-(4-methoxyphenyl)acetic acid (732 mg, 3.78 mmol, 2 equiv.), EDCi (844 mg, 4.36 mmol, 2 equiv.), triethylamine (603 μ L, 4.36 mmol, 2 equiv.), DMAP (0.03g, 0.22 mmol, 20 mol%) and DCM (35 mL). Purification was achieved by flash chromatography yielding ester **289** as a yellow solid (0.53g, 79%). Recrystallisation (Pet/DCM) afforded the title compound as yellow crystals.

MP: 74–76 °C; FTIR (film/ cm^{-1}) ν_{max} : 2941, 2838, 2264, 1769, 1735, 1612, 1512; ^1H NMR (300 MHz, CDCl_3) δ_{H} : 7.24–7.16 (2H, m), 6.91–6.82 (2H, m), 5.61 (1H, q, J = 6.8 Hz), 4.47–4.38 (2H, m), 3.93–3.84 (2H, m), 3.80 (3H, s), 3.57 (2H, s), 1.52 (3H, d, J = 6.8 Hz); ^{13}C NMR (75 MHz, CDCl_3) δ_{C} : 171.2, 159.1, 138.0, 130.7, 126.1, 114.4, 77.6, 70.6, 63.4, 61.4, 55.7, 47.1, 40.8, 21.7; MS (ESI:+ve) m/z : calcd for $\text{C}_{16}\text{H}_{18}\text{NO}_5$: 304.1185, found: 304.1190 $[\text{M} + \text{H}]^+$.

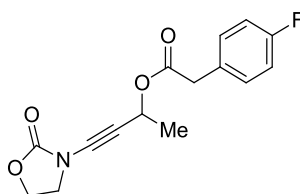
4-(2-Oxooxazolidin-3-yl)but-3-yn-2-yl 2-(4-(dimethylamino)phenyl)acetate (290)

Prepared according to general procedure C using; propargyl alcohol **266** (674 mg, 4.40 mmol, 1 equiv.), 2-(4-(dimethylamino)phenyl)acetic acid (1.57 g, 8.80 mmol, 2 equiv.), EDCi (1.73 g, 8.8 mmol, 2 equiv.), triethylamine (1.21 mL, 8.80 mmol, 2 equiv.), DMAP (106 mg, 0.88 mmol, 20 mol%) and DCM (60 mL). Purification was achieved

by flash chromatography yielding ester **290** as a yellow solid (0.93 g, 68%). Recrystallisation (Pet/DCM) afforded the title compound as yellow crystals.

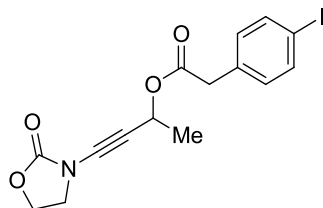
MP: 133–135 °C; FTIR (film/cm⁻¹) ν_{max} : 2982, 2890, 2268, 1773, 1735, 1615; ¹H NMR (250 MHz, CDCl₃) δ_{H} : 7.18–7.11 (2H, m), 6.73–6.65 (2H, m), 5.60 (1H, q, $J = 6.7$ Hz), 4.40 (2H, dd, $J = 7.6, 6.6$ Hz), 3.87 (2H, dd, $J = 7.6, 6.6$ Hz), 3.52 (2H, s), 2.92 (6H, s), 1.51 (3H, d, $J = 6.7$ Hz); ¹³C NMR (75 MHz, CDCl₃) δ_{C} : 171.2, 155.9, 129.9, 121.5, 122.8, 75.0, 70.3, 63.0, 60.8, 46.7, 40.7, 40.2, 21.4; MS (ESI:+ve) m/z : calcd for C₁₇H₂₁N₂O₄: 317.1501, found: 317.1498 [M + H]⁺

4-(2-Oxooxazolidin-3-yl)but-3-yn-2-yl 2-(4-fluorophenyl)acetate (**291**)



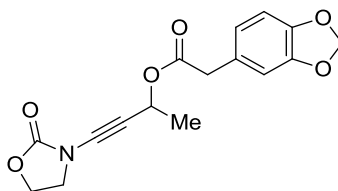
Prepared according to general procedure C using; propargyl alcohol **266** (674 g, 4.40 mmol, 1 equiv.), 2-(4-fluorophenyl)acetic acid (1.35 g, 8.80 mmol, 2 equiv.), EDCi (1.73 g, 8.80 mmol, 2 equiv.), triethylamine (1.21 mL, 8.80 mmol, 2 equiv.), DMAP (106 mg, 0.88 mmol, 20 mol%) and DCM (60 mL). Purification was achieved by flash chromatography yielding ester **291** as an amorphous yellow solid (0.72g, 57%).

FTIR (film/cm⁻¹) ν_{max} : 2982, 2890, 2267, 1769, 1734, 1603; ¹H NMR (250 MHz, CDCl₃) δ_{H} : 7.30–7.17 (2H, m), 7.05–6.94 (2H, m), 6.60 (1H, q, $J = 6.7$ Hz), 4.42 (2H, dd, $J = 8.0, 6.7$ Hz), 3.87 (2H, dd, $J = 8.0, 6.7$ Hz), 3.59 (2H, s), 1.51 (3H, d, $J = 6.7$ Hz); ¹³C NMR (75 MHz, CDCl₃) δ_{C} : 170.4, 162.0 (d, $J = 245.8$ Hz), 155.8, 130.9, 130.8, 129.4 (d $J = 4.6$ Hz), 115.4 (d, $J = 22.1$ Hz), 75.2, 70.0, 63.1, 61.2, 46.7, 40.4, 21.4; MS (ESI:+ve) m/z : calcd for C₁₅H₁₄FNNaO₄: 314.0805, found: 314.0787 [M + Na]⁺

4-(2-Oxooxazolidin-3-yl)but-3-yn-2-yl 2-(4-iodophenyl)acetate (292)

Prepared according to general procedure C using; propargyl alcohol **266** (342 mg, 2.21 mmol, 1 equiv.), 2-(4-iodophenyl)acetic acid (904 mg, 3.42 mmol, 2 equiv.), EDCi (843 mg, 3.42 mmol, 2 equiv.), triethylamine (598 mL, 3.42 mmol, 2 equiv.), DMAP (27 mg, 0.22 mmol, 20 mol%) and DCM (30 mL). Purification was achieved by flash chromatography yielding ester **292** as a yellow solid (0.62g, 71%). Recrystallisation (Pet/DCM) afforded the title compound as yellow crystals.

MP: 92–94 °C; FTIR (film/cm⁻¹) ν_{max} : 2988, 2263, 1766, 1732, 1589; ¹H NMR (300 MHz, CDCl₃) δ_{H} : 7.65 (2H, app.d, $J = 8.5$ Hz), 7.04 (2H, app. d, $J = 8.5$ Hz), 5.60 (1H, q, $J = 6.9$ Hz), 4.45 (1H, d, $J = 7.8$ Hz), 4.42 (1H, d, $J = 6.6$ Hz), 3.90 (1H, d, $J = 6.6$ Hz), 3.87 (1H, d, $J = 7.8$ Hz), 3.57 (2H, s), 1.51 (3H, d, $J = 6.9$ Hz); ¹³C NMR (75 MHz, CDCl₃) δ_{C} : 169.9, 155.9, 137.6, 133.3, 131.4, 92.7, 75.5, 69.9, 63.1, 61.3, 46.7, 40.7, 21.4; MS (ESI:+ve) m/z : calcd for: C₁₅H₁₄NO₄INa, 421.9866 found: 422.0001 [M + Na]⁺

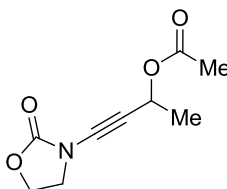
4-(2-Oxooxazolidin-3-yl)but-3-yn-2-yl 2-(benzo[d][1,3]dioxol-5-yl)acetate (293)

Prepared according to general procedure C using; propargyl alcohol **266** (671 g, 4.40 mmol, 1 equiv.), 2-(benzo[d][1,3]dioxol-5-yl)acetic acid (1.58 g, 8.80 mmol, 2 equiv.), EDCi (1.72 g, 8.80 mmol, 2 equiv.), triethylamine (1.21 mL, 8.80 mmol, 2 equiv.), DMAP (106 mg, 0.88 mmol, 20 mol%) and DCM (60 mL). Purification was achieved

by flash chromatography yielding ester **293** as a yellow solid (0.81 g, 60%). Recrystallisation (Pet/DCM) afforded the title compound as yellow crystals.

MP: 107–109 °C; FTIR (film/cm⁻¹) ν_{max} : 2982, 2890, 2267, 1768, 1733, 1613; ¹H NMR (250 MHz, CDCl₃) δ_{H} : 6.79–6.67 (3H, m), 5.93 (2H, s), 5.59 (1H, q, J = 6.7 Hz), 4.41 (2H, dd, J = 7.8, 6.7 Hz), 3.88 (2H, dd, J = 7.8, 6.7 Hz), 3.52 (2H, s), 1.51 (3H, d, J = 6.7 Hz); ¹³C NMR (75 MHz, CDCl₃) δ_{C} : 170.6, 155.9, 147.2, 146.8, 127.2, 122.5, 109.7, 108.3, 101.0, 75.2, 70.1, 63.0, 61.1, 46.7, 40.8, 21.4; MS (ESI:+ve) m/z : calcd for C₁₆H₁₅NNaO₆: 340.0797, found: 340.0776.

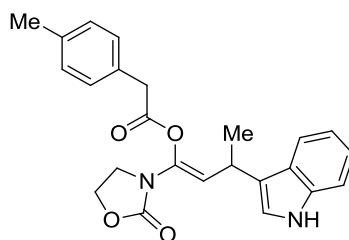
4-(2-Oxooxazolidin-3-yl)but-3-yn-2-yl acetate¹⁶¹ (**295**)



Acetic anhydride (356 μ L, 3.77 mmol, 1.1 equiv.), Et₃N (715 μ L, 5.15 mmol, 1.75 equiv.) and DMAP (42 mg, 0.34 mmol, 10 mol%) were added to a round bottomed flask containing DCM (20 mL). **266** (531mg, 3.43 mmol, 1 equiv.) in DCM (5 mL) was added and the reaction was allowed to stir at room temperature for 3 hours. Upon completion, the reaction was concentrated *in vacuo* and subjected to column chromatography, eluting with 2:1 Pet/EtOAc, affording **295** as a clear oil (603 mg, 89 %).

FTIR (thin film) ν_{max} : 2968, 2938, 2877, 2267, 1770, 1712; ¹H NMR (500 MHz, CDCl₃) δ_{H} : 5.59 (1H, q, J = 6.7 Hz), 4.46–4.42 (2H, m), 3.94–3.90 (2H, m), 2.07 (3H, s), 1.53 (3H, d, J = 6.7 Hz); ¹³C NMR (125 MHz, CDCl₃) δ_{C} : 169.9, 155.9, 74.9, 70.2, 63.0, 60.6, 46.7, 21.4, 21.1; HRMS (ESI, +ve) m/z : calcd. for C₉H₁₁NO₄Na: 220.0586, found: 220.0585 [M + Na]⁺.

(Z)-3-(1H-Indol-3-yl)-1-(2-oxooxazolidin-3-yl)but-1-en-1-yl 2-(*p*-tolyl)acetate (**296**)

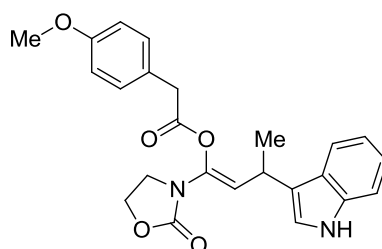


Prepared according to general procedure D using, indole (20 mg, 0.17 mmol, 1 equiv.), **288** (50 mg, 0.17 mmol, 1 equiv.), AuCl(PPh₃) (4.3 mg, 0.01 mmol, 5 mol%), AgPF₆ (2.2 mg, 0.01 mmol, 5 mol%) and DCM (2 mL). Purification by flash chromatography afforded enamide **296** as a light yellow oil (60 mg, 85%).

FTIR (thin film) ν_{max} : 3414, 2980, 2890, 1760, 1685; ¹H NMR (400 MHz, CDCl₃) δ_{H} : 7.95 (1H, br. s), 7.53 (1H, d, J = 7.9 Hz), 7.35 (1H, d, J = 7.9 Hz), 7.23–7.16 (3H, m), 7.15–7.06 (3H, m), 6.96 (1H, d, J = 1.9 Hz), 5.25 (1H, d, J = 9.7 Hz), 4.33–4.25 (2H, m), 3.77 (2H, s), 3.76–3.66 (3H, m), 2.33 (3H, s), 1.41 (3H, d, J = 7.1 Hz); ¹³C NMR (100 MHz, CDCl₃) δ_{C} : 169.6, 154.5, 137.2, 136.5, 136.3, 129.9, 1295, 129.3, 126.6, 122.1, 1203, 119.9, 119.4, 119.3, 114.7, 111.1, 61.7, 45.4, 40.3, 27.7, 21.1, 20.9; HRMS (ESI, +ve) m/z : calcd. for C₂₄H₂₄N₂O₄Na: 427.1634, found: 427.1695 [M + Na]⁺.

(Z)-3-(1H-Indol-3-yl)-1-(2-oxooxazolidin-3-yl)but-1-en-1-yl 2-(4-methoxyphenyl)acetate (297)

2-(4-

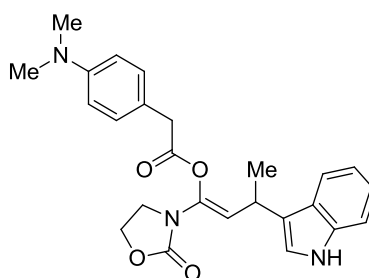


Prepared according to general procedure D using, indole (19 mg, 0.17 mmol, 1 equiv.), **289** (50 mg, 0.17 mmol, 1 equiv.), AuCl(PPh₃) (4.1 mg, 0.01 mmol, 5 mol%), AgPF₆ (2.1 mg, 0.01 mmol, 5 mol%) and DCM (2 mL). Purification by flash chromatography afforded enamide **297** as a light brown oil (51 mg, 74%).

FTIR (thin film) ν_{\max} : 3384, 2959, 2927, 1756, 1691, 1612; ^1H NMR (400 MHz, CDCl_3) δ_{H} : 8.08 (1H, br. s), 7.59 (1H, app. d, $J = 7.9$ Hz), 7.38 (1H, app. d, $J = 7.9$ Hz), 7.30–7.19 (2H, m), 7.16–7.11 (1H, m), 7.01–6.97 (1H, m), 6.95–6.85 (2H, m), 5.28 (1H, d, $J = 9.6$ Hz), 4.31 (2H, app. t, $J = 8.2$ Hz), 3.89–3.63 (8H, m), 1.46 (3H, d, $J = 7.0$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ_{C} : 169.8, 159.0, 154.6, 136.5, 136.3, 130.6, 126.5, 125.1, 122.0, 120.4, 119.8, 119.4, 119.3, 114.7, 114.2, 111.2, 61.8, 55.3, 45.4, 39.8, 27.7, 20.9; HRMS (ESI, +ve) m/z : calcd. for: $\text{C}_{24}\text{H}_{24}\text{N}_2\text{O}_5\text{Na}$, 443.1583 found: 443.1648 $[\text{M} + \text{Na}]^+$.

(Z)-3-(1H-Indol-3-yl)-1-(2-oxooxazolidin-3-yl)but-1-en-1-yl
(dimethylamino)phenyl)acetate (298)

2-(4-

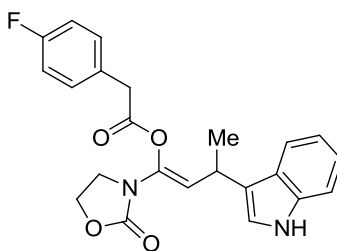


Prepared according to general procedure D using, indole (37 mg, 0.32 mmol, 1 equiv.), **290** (100 mg, 0.32 mmol, 1 equiv.), $\text{AuCl}(\text{PPh}_3)$ (7.8 mg, 0.02 mmol, 5 mol%), AgPF_6 (4.0 mg, 0.02 mmol, 5 mol%) and DCM (4 mL). Purification by flash chromatography afforded enamide **298** as a light yellow oil (119 mg, 87%).

FTIR (thin film) ν_{\max} : 3406, 2981, 2980, 1751, 1683, 1614, 1522; ^1H NMR (400 MHz, CDCl_3) δ_{H} : 8.01 (1H, br. s), 7.56 (1H, app. d, $J = 8.0$ Hz), 7.33 (1H, app. d, $J = 8.0$ Hz), 7.23–7.12 (3H, m), 7.08 (1H, app. t, $J = 7.5$ Hz), 6.95 (1H, d, $J = 1.8$ Hz), 6.68 (2H, app. d, $J = 8.6$ Hz), 5.30 (1H, d, $J = 9.7$ Hz), 4.26 (2H, app. t, $J = 8.1$ Hz), 3.80–3.61 (5H, m), 2.92 (6H, s), 1.41 (3H, d, $J = 7.0$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ_{C} : 170.1, 154.6, 149.8, 136.6, 136.2, 130.1, 126.5, 121.9, 120.9, 120.4, 119.8, 119.5, 119.3, 115.0, 113.0, 111.2, 61.8, 45.3, 40.8, 39.8, 27.7, 21.0; HRMS (ESI, +ve) m/z : calcd. for $\text{C}_{25}\text{H}_{28}\text{N}_3\text{O}_4$: 434.2080, found: 434.2084 $[\text{M} + \text{Na}]^+$.

(Z)-3-(1H-Indol-3-yl)-1-(2-oxooxazolidin-3-yl)but-1-en-1-yl 2-(4-fluorophenyl)acetate (299)

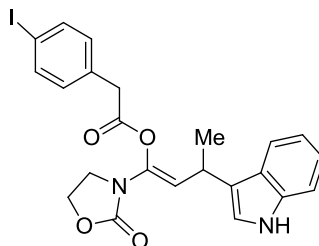
2-(4-



Prepared according to general procedure D using, indole (21 mg, 0.18 mmol, 1 equiv.), **291** (50 mg, 0.18 mmol, 1 equiv.), AuCl(PPh₃) (4.5 mg, 0.01 mmol, 5 mol%), AgPF₆ (2.3 mg, 0.01 mmol, 5 mol%) and DCM (2 mL). Purification by flash chromatography afforded enamide **299** as a light pink oil (55 mg, 79%).

FTIR (thin film) ν_{max} : 3383, 2959, 1924, 2854, 1754, 1696; ¹H NMR (400 MHz, CDCl₃) δ_{H} : 8.07 (1H, br. s), 7.60–7.56 (2H, m), 7.42–7.37 (1H, m), 7.33–7.27 (2H, m), 7.27–7.20 (1H, m), 7.17–7.12 (1H, m), 7.07–7.00 (2H, m), 7.00–6.99 (1H, m), 5.22 (1H, d, J = 9.1 Hz), 4.38–4.31 (2H, m), 3.83 (2H, s), 3.82–3.72 (3H, m), 1.46 (3H, d, J = 7.3 Hz); ¹³C NMR (100 MHz, CDCl₃) δ_{C} : 169.2, 154.3 (d, J = 245.4 Hz), 136.5 (d, J = 6.1 Hz), 134.2, (d, J = 15.3 Hz), 131.1 (d, J = 7.6 Hz), 128.8, 126.5, 122.1, 120.3, 119.7, 119.4, 119.3, 115.7, 115.5, 114.1, 111.2, 61.7, 45.5, 39.7, 27.7, 20.7; HRMS (ESI, +ve) m/z : calcd. for C₂₃H₂₁N₂O₄FNa: 431.1383, found: 431.1489 [M + Na]⁺.

(Z)-3-(1H-Indol-3-yl)-1-(2-oxooxazolidin-3-yl)but-1-en-1-yl 2-(4-iodophenyl)acetate (300)

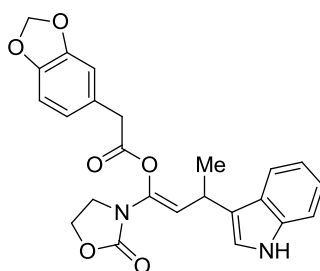


Prepared according to general procedure D using, indole (15 mg, 0.13 mmol, 1 equiv.), **292** (50 mg, 0.13 mmol, 1 equiv.), AuCl(PPh₃) (3 mg, 0.006 mmol, 5 mol%), AgPF₆

(1.6 mg, 0.006 mmol, 5 mol%) and DCM (2 mL). Purification by flash chromatography afforded enamide **300** as an orange solid (60 mg, 92%). Recrystallisation (Pet/DCM) afforded the title compound as orange crystals.

MP: 127–129 °C; FTIR (thin film) ν_{max} : 3261, 2971, 2911, 1772, 1720, 1683; ^1H NMR (400 MHz, CDCl_3) δ_{H} : 8.07 (1H, br. s), 7.67 (2H, app. d, $J = 8.4$ Hz), 7.59–7.55 (1H, m), 7.42–7.37 (1H, m), 7.27–7.22 (1H, m), 7.19–7.14 (1H, m), 7.07 (2H, app. d, $J = 8.4$ Hz), 7.01–7.00 (1H, m), 5.21 (1H, d, $J = 9.6$ Hz), 4.40–4.36 (2H, m), 3.79 (2H, s), 3.79–3.72 (3H, m), 1.47 (3H, d, $J = 7.0$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ_{C} : 168.8, 154.3, 137.8, 136.5, 134.3, 134.1, 132.6, 131.5, 129.4, 126.5, 122.1, 120.4, 119.7, 119.5, 119.3, 114.1, 111.3, 93.1, 61.7, 45.6, 40.1, 27.7, 21.1; HRMS (ESI, +ve) m/z : calcd. for $\text{C}_{23}\text{H}_{21}\text{N}_2\text{O}_4\text{INa}$: 539.0444, found: 539.0490 $[\text{M} + \text{Na}]^+$.

(Z)-3-(1H-Indol-3-yl)-1-(2-oxooxazolidin-3-yl)but-1-en-1-yl 2-(benzo[d][1,3]dioxol-5-yl)acetate (301)

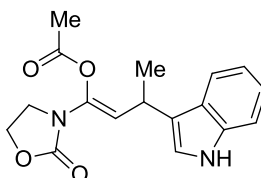


Prepared according to general procedure D using, indole (18 mg, 0.16 mmol, 1 equiv.), **293** (50 mg, 0.16 mmol, 1 equiv.), $\text{AuCl}(\text{PPh}_3)$ (4.0 mg, 0.01 mmol, 5 mol%), AgPF_6 (2.0 mg, 0.01 mmol, 5 mol%) and DCM (2 mL). Purification by flash chromatography afforded enamide **301** as a light brown oil (26 mg, 38%).

FTIR (thin film) ν_{max} : 3385, 2966, 1770, 1706; ^1H NMR (400 MHz, CDCl_3) δ_{H} : 8.03 (1H, br. s), 7.64–7.49 (2H, m), 7.39 (1H, app. d, $J = 8.0$ Hz), 7.26–7.18 (1H, m), 7.17–7.11 (1H, m), 7.01 (1H, app. d, $J = 1.8$ Hz), 6.85 (1H, s), 6.79 (1H, s), 5.98–5.94 (2H, m), 5.26 (1H, d, $J = 9.6$ Hz), 4.34 (2H, t, $J = 8.1$ Hz), 3.84–3.69 (5H, m), 1.47 (3H, d, $J = 7.0$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ_{C} : 169.6, 154.5, 147.9, 136.5, 136.4, 126.5, 122.7, 122.1, 120.4, 119.8, 119.3, 114.6, 111.2, 110.0, 108.5, 101.1, 61.7, 45.5, 40.3,

27.7, 20.9; HRMS (ESI, +ve) m/z : calcd. for, $C_{24}H_{22}N_2O_6Na$: 457.1376 found: 457.1411 $[M + Na]^+$.

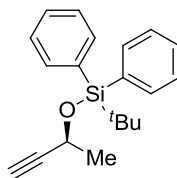
(Z)-3-(1H-Indol-3-yl)-1-(2-oxooxazolidin-3-yl)but-1-en-1-yl acetate (302)



Prepared according to general procedure D using, indole (30 mg, 0.25 mmol, 1 equiv.), **295** (50 mg, 0.25 mmol, 1 equiv.), $AuCl(PPh_3)$ (6.0 mg, 0.013 mmol, 5 mol%), $AgPF_6$ (5.0 mg, 0.013 mmol, 5 mol%) and DCM (2 mL). Purification by flash chromatography afforded enamide **302** as a brown oil (70 mg, 89%).

FTIR (thin film) ν_{max} : 3658, 3407, 2981, 2972, 2889, 1754, 1685, 1621; 1H NMR (500 MHz, $CDCl_3$) δ_H : 8.14 (1H, br.s), 7.69 (1H, d, $J = 7.7$ Hz), 7.36 (1H, d, $J = 7.7$ Hz), 7.20 (1H, app.t, $J = 7.5$ Hz), 7.13 (1H, app.t, $J = 7.5$ Hz), 7.01 (1H, d, $J = 1.6$ Hz), 5.19 (1H, d, $J = 9.6$ Hz), 4.31 (2H, app.t, $J = 8.3$ Hz), 3.95–3.86 (1H, m), 3.78–3.73 (2H, m), 2.27 (3H, s), 1.51 (3H, d, $J = 6.8$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C : 167.8, 154.4, 136.6, 136.4, 134.3, 126.6, 122.0, 120.4, 119.7, 119.3, 114.1, 111.3, 61.7, 45.5, 27.8, 20.8, 20.3; HRMS (ESI, +ve) m/z : calcd. for $C_{17}H_{18}N_2O_4Na$: 337.1164, found: 337.1176 $[M + Na]^+$.

(S)-(But-3-yn-2-yloxy)(tert-butyl)diphenylsilane ((S)-267)



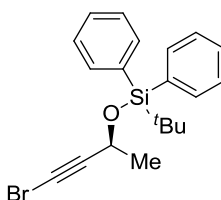
To a solution of (*S*)-3-butyn-2-ol (15.0 g, 214 mmol, 1 equiv.) in THF (200 mL) was added triethylamine (59.1 mL, 428 mmol, 2 equiv.), TBDPSCl (64.7g, 235 mmol, 1.1 equiv.) and DMAP (2.61 g, 21.4 mmol, 10 mol%). The resultant mixture was stirred at

rt for 18 h, diluted with hexane (300 mL) and washed with NH₄Cl (sat) (250 mL) and brine (250 mL) and dried over MgSO₄, filtered and concentrated *in vacuo*. Purification via flash chromatography, eluting with 100 % Pet, afforded (*S*)-**267** as a clear oil (66.0 g, 99 %).

$$[\alpha]_{\text{D}}^{20} = +65.0 \text{ (} c \text{ 1, DCM)}$$

All other data as previously stated.

(*S*)-((4-Bromobut-3-yn-2-yl)oxy)(*tert*-butyl)diphenylsilane ((*S*)-271)

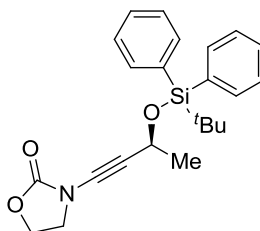


To a solution of the silyl ether (*S*)-**267** (66.0 g, 214 mmol, 1 equiv.) in acetone (250 mL) was added *N*-bromosuccinimide (41.6 g, 235 mmol, 1.1 equiv.) and AgNO₃ (3.63 g, 21.4 mmol, 10 mol%). The resultant mixture was stirred at rt for 3 h, diluted with CHCl₃ (250 mL), filtered through a pad of celite and concentrated *in vacuo*. Purification via flash chromatography, eluting with 100 % Pet, afforded the title compound as a light yellow oil (65.0 g, 78 %).

$$[\alpha]_{\text{D}}^{20} = +10.3 \text{ (} c \text{ 1, CH}_2\text{Cl}_2\text{)}$$

All other data as previously stated.

(*S*)-3-(3-((*tert*-Butyldiphenylsilyl)oxy)but-1-yn-1-yl)oxazolidin-2-one ((*S*)-274)

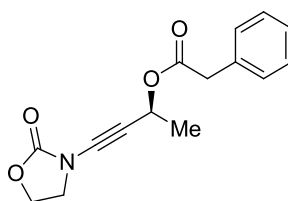


To a solution of the bromo-alkyne (**S**)-**271** (5.00 g, 12.9 mmol, 1.1 equiv.) and oxazolidinone (1.02 g, 11.8 mmol, 1 equiv.) in toluene (250 mL) was added $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ (586 mg, 2.35 mmol, 20 mol%), 1,10-phenanthroline (847 mg, 4.70 mmol, 40 mol%) and K_3PO_4 (4.99 g, 23.5 mmol, 2 equiv.). The suspension was then refluxed for 48 h, filtered through celite and concentrated *in vacuo*. Purification via flash chromatography, eluting with 4:1 Pet/EtOAc, afforded ynamide (**S**)-**274** as a white powder (3.14 g, 68%).

$$[\alpha]_{\text{D}}^{20} = -115.5 \text{ (} c \text{ 2, CHCl}_3 \text{)}$$

All other data as previously stated.

(S)-4-(2-Oxooxazolidin-3-yl)but-3-yn-2-yl 2-phenylacetate ((S)-264)

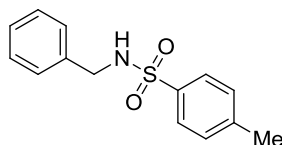


To a solution of the protected ynamide (**S**)-**274** (3.00g, 7.60 mmol, 1 equiv.) in THF (175 mL) was added TBAF (1M in THF, 15.2 mL, 15.2 mmol, 2 equiv.) at 0 °C. The resultant solution was then warmed to rt, after 40 min the reaction mixture was hydrolysed with NH_4Cl (sat) (25 mL) and extracted with EtOAc (3 × 25 mL). The combined extracts were dried over MgSO_4 , filtered and concentrated *in vacuo*. The crude material was passed through silica gel, eluting with 100% EtOAc, and used without further purification. To a solution of EDCi (1.80g, 9.43 mmol, 2 equiv.) in DCM (70 mL) was successively added triethylamine (1.31 mL, 9.43 mmol, 2 equiv.), DMAP (115 mg, 0.94 mmol, 20 mol%), phenylacetic acid (1.28g, 9.43 mmol, 2 equiv.) and crude propargylic alcohol (**S**)-**266**. After 3 hours at room temperature the resultant solution was washed with 10% citric acid (3 x 10 ml), NaHCO_3 (sat) (3 x 10 ml) and brine (10 ml). The organic extract was then dried over MgSO_4 and concentrated *in vacuo*. The crude mixture was then subjected to column chromatography, eluting with 4:1 Pet/EtOAc, to afford the title compound as a white solid (888 mg, 43% over two steps).

$[\alpha]_{\text{D}}^{20} = -122$ (c 1, CHCl_3)

All data as previously stated.

***N*-Benzyl-4-methylbenzenesulfonamide¹⁹³ (268)**

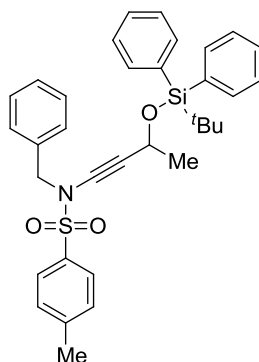


To benzylamine (10.4 mL, 96 mmol, 1 equiv.) and triethylamine (20 mL, 143 mmol, 1.5 equiv.) in DCM (500 mL), was added 4-methylbenzene-1-sulfonyl chloride (18.2 g, 96 mmol, 1 equiv.) in small portions. The reaction was allowed to stir at room temperature for 1 hour before being quenched by water (300 mL). The aqueous layer was extracted with dichloromethane (3 x 200 mL), then the organic extracts were combined, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was recrystallised (DCM/Petroleum ether) to afford **268** as a colourless crystals (25.0g, 99%).

^1H NMR (300 MHz, $(\text{CD}_3)_2\text{CO}$) δ_{H} : 7.67 (2H, app. d, $J = 8.4$ Hz), 7.29 (2H, app. d, $J = 8.4$ Hz), 7.21–7.07 (5H, m), 6.76 (1H, br. t, $J = 6.5$ Hz), 4.00 (2H, d, $J = 6.5$ Hz), 2.32 (3H, s); ^{13}C NMR (75 MHz, CDCl_3) δ_{C} : 144.2, 139.2, 139.0, 130.8, 129.6, 129.1, 128.5, 128.3, 48.1, 21.8.

All other data in accordance with literature precedence.¹⁹³

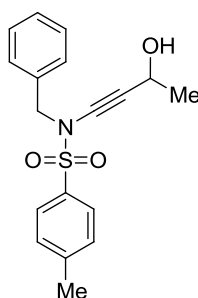
***N*-Benzyl-*N*-(3-((*tert*-butyldiphenylsilyl)oxy)but-1-yn-1-yl)-4-methylbenzenesulfonamide (313)**



To a solution of **268** (962 mg, 3.68 mmol, 1 equiv.) in pyridine (16 mL) at 0 °C was added KHMDS (1M in THF, 3.68 mL, 3.68 mmol, 1 equiv.) over 4 minutes. The reaction was allowed to stir for 10 minutes before a solution of CuI (702 mg, 3.68 mmol, 1 equiv.) in pyridine (8 mL) was added. The reaction mixture was allowed to warm to room temperature and stirred for 2 hours. A solution of **272** (2.85 g, 7.37 mmol, 2 equiv.) in toluene (12 mL) was then added over 1 hour, with the resultant mixture being allowed to stir for 20 hours. The reaction was then diluted with Et₂O (50 mL) and washed with 2:1 brine/concentrated NH₄OH (3 x 50 mL). The combined aqueous washings were then extracted with Et₂O (50 mL). The organic extracts were combined, dried with MgSO₄, filtered and concentrated *in vacuo*. Purification was achieved by flash chromatography (8:1 Pet/EtOAc) to afford the title compound as a yellow oil (1.51g, 72%).

FTIR (thin film) ν_{max} : 3071, 2956, 2930, 2890, 2857, 2246, 1597; ¹H NMR (300 MHz, CDCl₃) δ_{H} : 7.72–7.50 (6H, m), 7.41–7.04 (13H, m), 4.45 (1H, q, J = 6.5 Hz), 4.32 (1H, d, J = 13.6 Hz), 4.20 (1H, d, J = 13.6 Hz), 2.35 (3H, s), 1.25 (3H, d, J = 6.5 Hz), 0.96 (9H, s); ¹³C NMR (75 MHz, CDCl₃) δ_{C} : 144.5, 136.0, 135.8, 134.9, 133.8, 129.7, 128.7, 128.5, 128.2, 127.8, 127.7, 127.6, 77.6, 73.7, 60.2, 55.4, 26.9, 25.2, 21.7, 19.3; HRMS (ESI, +ve) m/z : calcd. for C₃₄H₃₈NOSSi: 568.2342, found: 568.2356 [M + Na]⁺.

***N*-Benzyl-*N*-(3-hydroxybut-1-yn-1-yl)-4-methylbenzenesulfonamide (314)**

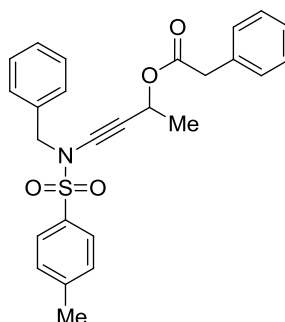


To a solution of **313** (1.51 g, 2.67 mmol, 1 equiv.) in THF (75 mL) was added TBAF (1M in THF, 5.34 mL, 5.34 mmol, 2 equiv.) at 0 °C. The resultant solution was then warmed to rt, after 40 min the reaction mixture was hydrolysed with NH₄Cl (sat) (25 mL) and extracted with EtOAc (3 x 25 mL). The combined extracts were dried over MgSO₄, filtered and concentrated *in vacuo*. The crude material was purified by rapid

filtration through silica gel, eluting with 2:1 Pet/EtOAc, to give alcohol **314** as a yellow oil (527 mg, 60%).

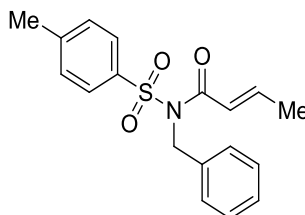
FTIR (film/cm⁻¹) ν_{\max} : 3375, 3035, 2983, 2930, 2245, 1596; ¹H NMR (300 MHz, CDCl₃) δ_{H} : 7.70–7.64 (2H, m), 7.35–7.15 (7H, m), 4.51–4.36 (3H, m), 2.36 (3H, s), 1.24 (3H, d, J = 6.7 Hz); ¹³C NMR (75 MHz, CDCl₃) δ_{C} : 144.7, 134.8, 134.6, 124.4, 129.7, 128.9, 128.5, 128.4, 127.7, 77.8, 73.5, 58.4, 55.4, 24.2, 21.6, 19.0; MS (ESI:+ve) m/z : calcd for C₁₈H₁₉NO₃SNa: 352.0984, found: 352.1113 [M + Na⁺].

4-(*N*-Benzyl-4-methylphenylsulfonamido)but-3-yn-2-yl 2-phenylacetate (**315**)



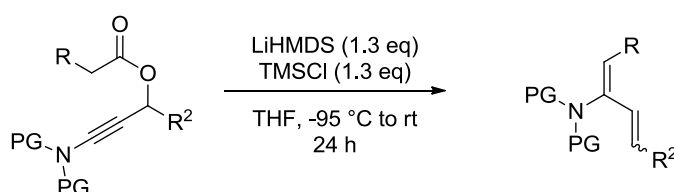
Prepared according to general procedure C, using **314** (527 mg, 1.60 mmol, 1 equiv.), phenylacetic acid (435 mg, 3.20 mmol, 2 equiv.), EDCi (613 mg, 3.20 mmol, 2 equiv.), NEt₃ (445 μ L, 3.20 mmol, 2 equiv.), DMAP (39 mg, 0.32 mmol, 20 mol%), DCM (75 mL). Purification was achieved by flash chromatography, eluting with 8:1 Pet/EtOAc, affording the title compound as a yellow oil (489 mg, 68%).

FTIR (film/cm⁻¹) ν_{\max} : 3030, 2990, 2246, 1736, 1597; ¹H NMR (300 MHz, CDCl₃) δ_{H} : 7.72 (2H, app. d, J = 8.5 Hz), 7.36–7.17 (12H, m), 5.47 (1H, q, J = 6.6 Hz), 4.51 (1H, d, J = 14.3 Hz), 4.40 (1H, d, J = 14.3 Hz), 3.57 (2H, s), 2.43 (3H, s), 1.36 (3H, d, J = 6.6 Hz); ¹³C NMR (75 MHz, CDCl₃) δ_{C} : 170.4, 144.6, 134.5, 134.3, 133.8, 129.7, 129.2, 128.9, 128.6, 128.5, 128.3, 127.8, 127.1, 78.8, 70.6, 61.2, 55.4, 41.2, 21.7, 21.1; MS (ESI:+ve) m/z : calcd for C₂₆H₂₅NO₄SNa: 470.1402, found: 470.1432 [M + Na⁺].

(E)-N-Benzyl-N-tosylbut-2-enamide (316)

Prepared according to general procedure D, using **315** (100 mg, 0.22 mmol, 1 equiv.), AuCl(PPh₃) (5.4 mg, 0.01 mmol, 5 mol%), AgPF₆ (2.8 mg, 0.01 mmol, 5 mol%) and DCM (4 mL). Purification by flash chromatography afforded **316** as a light orange oil (70 mg, 95%, 6:1 *E/Z*).

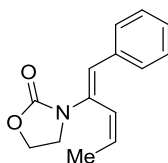
FTIR (film/cm⁻¹) ν_{\max} : 3031, 2974, 1708, 1683, 1635, 1597; ¹H NMR (500 MHz, CDCl₃) δ_{H} Major isomer: 7.70–7.65 (2H, m), 7.44–7.28 (7H, m), 7.00 (1H, dq, *J* = 15.0, 7.0 Hz), 6.63 (1H, dq, *J* = 15.0, 7.0 Hz), 5.13 (2H, s), 2.44 (3H, s), 1.85 (3H, dd, *J* = 7.0, 1.7 Hz); δ_{H} Minor isomer: 7.70–7.65 (2H, m), 7.44–7.28 (7H, m), 6.40 (1H, dq, *J* = 11.6, 7.0 Hz), 6.21 (1H, dq, *J* = 11.6, 7.0 Hz), 5.13 (2H, s), 2.44 (3H, s), 1.90 (3H, dd, *J* = 7.0, 1.7 Hz); ¹³C NMR (75 MHz, CDCl₃) δ_{C} Major isomer: 177.6, 166.0, 146.7, 144.7, 136.8, 133.7, 129.6, 129.4, 128.7, 127.8, 122.9, 41.1, 21.5, 18.5; δ_{C} Minor isomer: 177.6, 166.0, 146.5, 144.7, 136.8, 133.7, 129.6, 129.3, 128.7, 127.8, 122.0, 41.1, 21.6, 15.8; MS (ESI:+ve) *m/z*: calcd for C₁₈H₁₉NO₃SNa: 352.0984, found: 352.1095, [M + Na]⁺.

5.4 Chapter 4*5.4.1 General procedure E for the Ireland-Claisen rearrangement*

To a roundbottomed flask was added LiHMDS (1.3 equiv.) and TMSCl (1.3 equiv.). The mixture was allowed to stir at -95 °C for 15 min before the dropwise addition of

ynamido ester (0.37 mmol) in THF (2 ml). After 30 min at -95 °C, the reaction mixture was allowed to warm to rt after which it was allowed to stir for 24 hours. The reaction was then quenched with 1:1 1M HCl/Brine solution (5 ml) and extracted with EtOAc (3 x 10 ml), with the combined organic extracts being dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification via flash chromatography (petroleum ether: ethyl acetate = 2: 1) afforded the decarboxylated product.

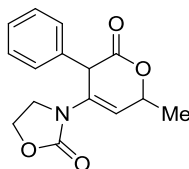
3-((1*E*,3*Z*)-1-phenylpenta-1,3-dien-2-yl)oxazolidin-2-one (335)



Prepared according to general procedure E using; ynamido ester **263** (100 mg, 0.37 mmol, 1 equiv.), LiHMDS (1 M in THF, 480 μ L, 0.48 mmol, 1.3 equiv.), TMSCl (41 μ L, 0.48 mmol, 1.3 equiv.) and THF (2mL). Purification was achieved by flash chromatography to give diene **335** as a yellow oil (51 mg, 61 %).

FTIR (film/ cm^{-1}) ν_{max} : 3025, 2916, 1744, 1620; ¹H NMR (250 MHz, CDCl₃) δ_{H} 7.32–7.07 (5H, m), 6.48 (1H, s), 6.03 (1H, dqd, J = 11.5, 1.7, 0.4 Hz), 5.74 (1H, dqd, J = 11.5, 7.2, 0.4 Hz), 4.36–4.31 (2H, m), 3.78–3.73 (2H, m), 1.50 (3H, dd, J = 7.2, 1.7 Hz); ¹³C NMR (75 MHz, CDCl₃) δ_{C} 156.1, 136.3, 132.5, 132.1, 129.3, 128.5, 127.3, 123.5, 123.1, 61.9, 46.3, 15.2; MS (ESI:+ve) m/z : calcd for C₁₄H₁₆NO₂ : 230.1181, found: 230.1174 [M + H]⁺.

3-(6-Methyl-2-oxo-3-phenyl-3,6-dihydro-2H-pyran-4-yl)oxazolidin-2-one (348)

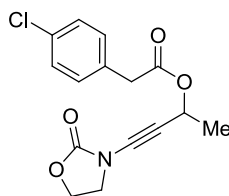


Prepared according to general procedure E using; ynamido ester **263** (100 mg, 0.38 mmol), LiHMDS (1M in THF, 0.40 mL, 0.40 mmol, 1.05 equiv.), TMSCl (51 μ L, 0.40

mmol, 1.05 equiv.) and THF (2 mL). Purification by flash chromatography afforded the title compound as a clear oil (26 mg, 30 %).

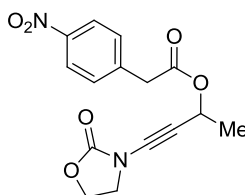
FTIR (film/cm⁻¹) ν_{max} : 2980, 2918, 1760, 1710, 1629; ¹H NMR (500 MHz, CDCl₃) δ_{H} 7.42–7.30 (5H, m), 5.80 (1H, d, J = 2.0 Hz), 5.31 (1H, d, J = 2.0 Hz), 5.20 (1H, qd, J = 6.9, 2.0 Hz), 4.34–4.29 (2H, m), 3.80–3.73 (1H, m), 3.73–3.65 (1H, m), 1.52 (3H, d, J = 6.9 Hz); ¹³C NMR (125 MHz, CDCl₃) δ_{C} 169.2, 154.3, 133.6, 129.2, 128.3, 127.7, 126.2, 111.3, 73.5, 61.4, 46.1, 44.5, 22.1; MS (ESI:+ve) m/z : calcd for C₁₅H₁₆NO₄: 274.1079, found: 274.1069, [M + H]⁺.

4-(2-Oxooxazolidin-3-yl)but-3-yn-2-yl 2-(4-chlorophenyl)acetate (**349**)



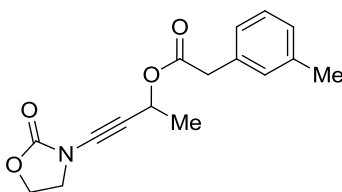
Prepared according to general procedure C using; propargyl alcohol **265** (540 mg, 3.61 mmol, 1 equiv.), 2-(4-chlorophenyl)acetic acid (1.21 g, 7.11 mmol, 2 equiv.), EDCI (1.36 g, 7.1 mmol, 2 equiv.), NEt₃ (988 μ L, 7.1 mmol, 2 equiv.), DMAP (87 mg, 0.71 mmol, 20 mol%) and DCM (50 mL). Purification was achieved by flash chromatography affording ester **349** as a pink oil (922 mg, 85%).

FTIR (film/cm⁻¹) ν_{max} : 2989, 2921, 2264, 1769, 1734; ¹H NMR (300 MHz, CDCl₃) δ_{H} 7.25–7.12 (4H, m), 5.53 (1H, q, J = 6.7 Hz), 4.38–4.32 (2H, m), 3.81–3.77 (2H, m), 3.52 (2H, s), 1.44 (3H, d, J = 6.7 Hz); ¹³C NMR (75 MHz, CDCl₃) δ_{C} 170.5, 156.2, 133.5, 132.5, 131.1, 129.1, 75.6, 70.4, 63.4, 61.7, 47.1, 40.9, 21.7; MS (ESI:+ve) m/z : calcd for C₁₅H₁₄NO₄Cl: 330.0509, found: 330.0494, [M + H]⁺.

4-(2-Oxooxazolidin-3-yl)but-3-yn-2-yl 2-(4-nitrophenyl)acetate (350)

Prepared according to general procedure C using; propargyl alcohol **265** (540 mg, 3.61 mmol, 1 equiv.), 2-(4-nitrophenyl)acetic acid (1.28 g, 7.11 mmol, 2 equiv.), EDCi (1.36 g, 7.11 mmol, 2 equiv.), NEt₃ (988 μ L, 7.11 mmol, 2 equiv.), DMAP (87 mg, 0.71 mmol, 20 mol%) and DCM (50 mL). Purification was achieved by flash chromatography affording ester **350** as an orange solid (920 mg, 82%).

FTIR (film/cm⁻¹) ν_{max} : 2985, 2265, 1768, 1736, 1606; ¹H NMR (300 MHz, CDCl₃) δ_{H} 8.16–8.13 (2H, m), 7.42–7.38 (2H, m), 5.56 (1H, q, J = 6.7 Hz), 4.39–4.34 (2H, m), 3.86–3.82 (2H, m), 3.49 (2H, s), 1.46 (3H, d, J = 6.7 Hz); ¹³C NMR (75 MHz, CDCl₃) δ_{C} 169.5, 156.2, 147.7, 141.4, 130.7, 124.2, 75.9, 70.2, 63.4, 62.1, 47.0, 41.3, 21.7; MS (ESI:+ve) m/z : calcd for C₁₅H₁₄N₂O₆: 341.0750, found: 341.0718, [M + H]⁺

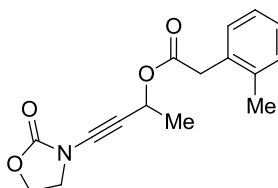
4-(2-Oxooxazolidin-3-yl)but-3-yn-2-yl 2-(*m*-tolyl)acetate (351)

Prepared according to general procedure C using; propargyl alcohol **265** (733 mg, 4.69 mmol, 1 equiv.), 2-(*m*-tolyl)acetic acid (1.41 g, 9.39 mmol, 2 equiv.), EDCi (1.79 g, 9.39 mmol, 2 equiv.), NEt₃ (1.31 mL, 9.39 mmol, 2 equiv.), DMAP (115 mg, 0.94 mmol, 20 mol%) and DCM (100 mL). Purification was achieved by flash chromatography affording ester **351** as a yellow oil (803 mg, 60%).

FTIR (film/cm⁻¹) ν_{max} : 3022, 2921, 2266, 1769, 1733, 1608; ¹H NMR (300 MHz, CDCl₃) δ_{H} : 7.25–7.19 (1H, m), 7.13–7.06 (3H, m), 5.62 (1H, q, J = 6.8 Hz), 4.46–4.39

(2H, m), 3.92–3.86 (2H, m), 3.60 (2H, s), 2.35 (3H, s), 1.53 (3H, d, $J = 6.8$ Hz); ^{13}C NMR (75 MHz, CDCl_3) δ_{C} : 170.7, 155.9, 138.2, 133.6, 130.1, 128.5, 127.9, 126.3, 75.1, 70.2, 63.1, 46.7, 41.2, 21.4; MS (ESI:+ve) m/z : calcd for $\text{C}_{16}\text{H}_{17}\text{NO}_4\text{Na}$: 310.1055, found: 310.1045, $[\text{M} + \text{Na}]^+$

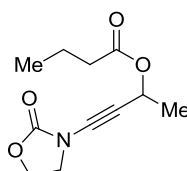
4-(2-Oxooxazolidin-3-yl)but-3-yn-2-yl 2-(*o*-tolyl)acetate (**352**)



Prepared according to general procedure C using; propargyl alcohol **265** (0.733 g, 4.69 mmol, 1 equiv.), 2-(*o*-tolyl)acetic acid (1.41 g, 9.39 mmol, 2 equiv.), EDCi (1.79 g, 9.39 mmol, 2 equiv.), NEt_3 (1.31 mL, 9.39 mmol, 2 equiv.), DMAP (115 mg, 0.94 mmol, 20 mol%) and DCM (100 mL). Purification was achieved by flash chromatography affording ester **352** as a yellow oil (744 mg, 56%).

FTIR (film/ cm^{-1}) ν_{max} : 3020, 2916, 2264, 1762, 1735, 1607; ^1H NMR (300 MHz, CDCl_3) δ_{H} : 7.23–7.14 (4H, m), 5.63 (1H, q, $J = 6.8$ Hz), 4.42 (2H, app. t, $J = 7.9$ Hz), 3.88 (2H, app. t, $J = 7.9$ Hz), 3.66 (2H, s), 2.33 (3H, s), 1.53 (3H, d, $J = 6.8$ Hz); ^{13}C NMR (75 MHz, CDCl_3) δ_{C} : 170.6, 156.0, 136.9, 132.5, 130.3, 130.2, 127.5, 126.2, 75.1, 70.2, 63.0, 61.0, 46.7, 39.2, 21.3, 19.5; MS (ESI:+ve) m/z : calcd for: 310.1055, found: 310.1059, $[\text{M} + \text{Na}]^+$

4-(2-Oxooxazolidin-3-yl)but-3-yn-2-yl butyrate (**353**)

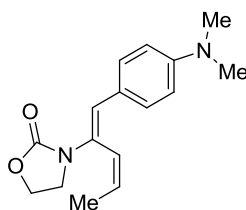


Prepared according to general procedure C using; propargyl alcohol **265** (872 mg, 5.80 mmol, 1 equiv.), butyric acid (1.12 mL, 11.5 mmol, 2 equiv.), EDCi (2.22 g, 11.5

mmol, 2 equiv.), triethylamine (1.61 mL, 11.5 mmol, 2 equiv.), DMAP (146 mg, 1.20 mmol, 20 mol%) and DCM (60 mL). Purification was achieved by flash chromatography yielding ester **353** as a yellow oil (833 mg, 65%).

FTIR (film/cm⁻¹) ν_{\max} : 2968, 2938, 2878, 2268, 1770, 1733, 1712; ¹H NMR (250 MHz, CDCl₃) δ_{H} 5.60 (1H, q, $J = 6.7$ Hz), 4.49–4.43 (2H, m), 3.93–3.88 (2H, m), 2.28 (2H, t, $J = 7.5$ Hz), 1.65 (2H, sx, $J = 7.5$ Hz), 1.51 (3H, d, $J = 6.7$ Hz), 0.94 (3H, t, $J = 7.5$ Hz); ¹³C NMR (75 MHz, CDCl₃) δ_{C} 172.9, 156.3, 75.2, 70.7, 63.5, 60.6, 47.1, 36.5, 21.8, 18.7, 14.0; MS (ESI:+ve) m/z : calcd for C₁₁H₁₅NNaO₄: 248.0899, found 248.0892 [M + Na]⁺.

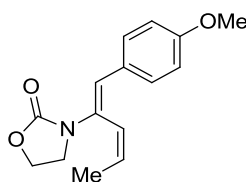
3-((1*E*,3*Z*)-1-(4-(Dimethylamino)phenyl)penta-1,3-dien-2-yl)oxazolidin-2-one (**354**)



Prepared according to general procedure E using; ynamido ester **289** (100 mg, 0.35 mmol, 1 equiv.), LiHMDS (1 M in THF, 570 μ L, 0.57 mmol, 1.8 equiv.), TMSCl (73 μ L, 0.57 mmol, 1.8 equiv.) and THF (2mL). Purification was achieved by flash chromatography to give diene **354** as a yellow oil (51 mg, 53 %).

FTIR (film/cm⁻¹) ν_{\max} : 2903, 2798, 1741, 1604, 1519; ¹H NMR (500 MHz, CDCl₃) δ_{H} : 7.29 (2H, app. d, $J = 8.5$ Hz), 6.65 (2H, app. d, $J = 8.5$ Hz), 6.48 (1H, s), 6.17–6.08 (1H, m), 5.79 (1H, dqd, $J = 11.4, 7.2, 0.8$ Hz), 4.42–4.34 (2H, m), 3.82–3.75 (2H, m), 2.96 (6H, s), 1.66 (3H, dd, $J = 7.2, 1.8$ Hz); ¹³C NMR (75 MHz, CDCl₃) δ_{C} : 156.1, 149.5, 146.8, 130.3, 130.2, 128.5, 125.2, 123.8, 111.9, 61.6, 46.2, 40.4, 14.7; MS (ESI:+ve) m/z : calcd for C₁₆H₂₀N₂O₂Na: 295.1422, found: 295.1417, [M + Na]⁺.

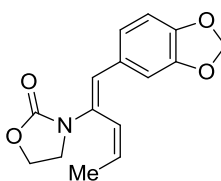
3-((1*E*,3*Z*)-1-(4-Methoxyphenyl)penta-1,3-dien-2-yl)oxazolidin-2-one (**355**)



Prepared according to general procedure E using; ynamido ester **288** (100 mg, 0.33 mmol, 1 equiv.), LiHMDS (1 M in THF, 602 μL , 0.60 mmol, 1.8 equiv.), TMSCl (76 μL , 0.60 mmol, 1.8 equiv.) and THF (2mL). Purification was achieved by flash chromatography to give diene **355** as a yellow oil (63 mg, 73 %, 3:1 *E/Z*).

FTIR (film/ cm^{-1}) ν_{max} : 2980, 2905, 2836, 1747, 1604, 1571; ^1H NMR (500 MHz, CDCl_3) δ_{H} (*Z* isomer): 7.31 (2H, app. d, $J = 8.5$ Hz), 6.82 (2H, app. d, $J = 8.5$ Hz), 6.52 (1H, s), 6.13–6.04 (1H, m), 5.87–5.74 (1H, m), 4.42–4.35 (2H, m), 3.83–3.80 (4H, m), 3.78 (1H, d, $J = 7.8$ Hz), 1.61 (3H, dd, $J = 7.1, 1.9$ Hz); δ_{H} (*E* isomer): 7.31 (2H, app. d, $J = 8.5$ Hz), 6.82 (2H, app. d, $J = 8.5$ Hz), 6.35 (1H, s), 6.28–6.17 (1H, m), 5.85–5.69 (1H, m), 4.36–4.27 (2H, m), 3.72–3.67 (5H, m), 1.73 (3H, dd, $J = 6.8, 1.7$ Hz); ^{13}C NMR (75 MHz, CDCl_3) δ_{C} : 158.6, 155.9, 131.3, 130.4, 130.3, 128.4, 123.4, 123.3, 113.6, 61.5, 55.2, 46.0, 14.7; MS (ESI:+ve) m/z : calcd for $\text{C}_{15}\text{H}_{18}\text{NO}_3$: 260.1287, found: 260.1282, $[\text{M} + \text{H}]^+$

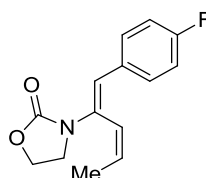
3-((1*E*,3*Z*)-1-(Benzo[*d*][1,3]dioxol-5-yl)penta-1,3-dien-2-yl)oxazolidin-2-one (356)



Prepared according to general procedure E using; ynamido ester **292** (100 mg, 0.35 mmol, 1 equiv.), LiHMDS (1 M in THF, 572 μL , 0.57 mmol, 1.8 equiv.), TMSCl (73 μL , 0.57 mmol, 1.8 equiv.) and THF (2mL). Purification was achieved by flash chromatography to give diene **356** as a yellow oil (64 mg, 69 %, 2:1 *E/Z*).

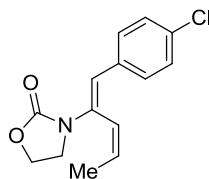
FTIR (film/cm⁻¹) ν_{\max} : 2907, 1741, 1604; ¹H NMR (500 MHz, CDCl₃) δ_{H} (*Z* isomer): 6.97–6.92 (1H, m), 6.91–6.71 (2H, m), 6.49 (1H, app. s), 6.11–6.03 (1H, m), 5.95 (2H, s), 5.89–5.76 (1H, m), 4.40–4.35 (2H, m), 3.82–3.75 (2H, m), 1.62 (3H, dd, $J = 7.1, 1.8$ Hz); δ_{H} (*E* isomer): 6.97–6.92 (1H, m), 6.91–6.71 (2H, m), 6.36 (1H, s), 6.31 δ_{H} (*E* isomer): 6.97–6.92 (1H, m), 6.91–6.71 (2H, m), 6.22 (1H, m), 5.90 (2H, s), 5.86–5.76 (1H, m), 4.41–4.33 (2H, m), 3.80–3.73 (2H, m), 1.78 (3H, dd, $J = 6.8, 1.7$ Hz); ¹³C NMR (75 MHz, CDCl₃) δ_{C} 155.8, 147.4, 146.6, 131.7, 130.8, 129.9, 123.4, 123.3, 123.2, 108.8, 108.1, 101.0, 61.5, 45.9, 14.7; MS (ESI:+ve) m/z : calcd for C₁₅H₁₆NO₄: 274.1079, found: 274.107, [M + H]⁺

3-((1*E*,3*Z*)-1-(4-Fluorophenyl)penta-1,3-dien-2-yl)oxazolidin-2-one (357)



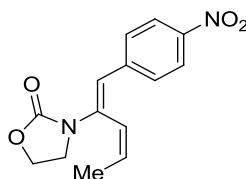
Prepared according to general procedure E using; ynamido ester **290** (100 mg, 0.35 mmol, 1 equiv.), LiHMDS (1 M in THF, 632 μ L, 0.63 mmol, 1.8 equiv.), TMSCl (79 μ L, 0.63 mmol, 1.8 equiv.) and THF (2mL). Purification was achieved by flash chromatography to give diene **357** as a yellow oil (62 mg, 67 %, 3:1 *E/Z*).

FTIR (film/cm⁻¹) ν_{\max} : : 2964, 2934, 2874, 1746, 1643; ¹H NMR (500 MHz, CDCl₃) δ_{H} (*Z* isomer): 7.34–7.19 (2H, m), 6.96–6.83 (2H, m), 6.47 (1H, app. s), 5.98 (1H, app. d, $J = 11.4$ Hz), 5.75 (1H, dq, $J = 11.4, 7.0$ Hz), 4.38–4.25 (2H, m), 3.79–3.69 (2H, m), 1.49 (3H, dd, $J = 7.0, 1.6$ Hz); δ_{H} (*E* isomer): 7.34–7.19 (2H, m), 6.96–6.83 (2H, m), 6.54 (1H, s), 6.29 (1H, app. d, $J = 15.4$ Hz), 6.02–5.86 (1H, m), 4.51–4.41 (2H, m), 3.90–3.81 (2H, m), 1.83 (3H, dd, $J = 6.8, 1.7$ Hz); ¹³C NMR (75 MHz, CDCl₃) δ_{C} : 161.6 (d, $J = 245.9$ Hz), 155.8, 132.1, 132.0, 131.9, 130.5 (d, $J = 9.0$ Hz), 122.9, 121.6, 115.1 (d, $J = 21.5$ Hz), 61.5, 45.9, 14.7; MS (ESI:+ve) m/z : calcd for: C₁₄H₁₄NO₂F, 248.1087 found: 248.1094, [M + H]⁺.

3-((1*E*,3*Z*)-1-(4-Chlorophenyl)penta-1,3-dien-2-yl)oxazolidin-2-one (358)

Prepared according to general procedure E using; ynamido ester **349** (100 mg, 0.35 mmol, 1 equiv.), LiHMDS (1 M in THF, 591 μ L, 0.59 mmol, 1.8 equiv.), TMSCl (75 μ L, 0.59 mmol, 1.8 equiv.) and THF (2mL). Purification was achieved by flash chromatography to give diene **358** as a yellow oil (53 mg, 56 %, 4:1 *E/Z*).

FTIR (film/ cm^{-1}) ν_{max} : 2906, 1738, 1607, 1517; ^1H NMR (500 MHz, CDCl_3) δ_{H} : 7.33–7.19 (4H, m), 6.52 (1H, s), 6.10–6.02 (1H, m), 5.83 (1H, app. dq, $J = 11.4, 7.1$ Hz), 4.41 (1H, d, $J = 7.8$ Hz), 4.38 (1H, d, $J = 6.6$ Hz), 3.83 (1H, d, $J = 6.6$ Hz), 3.80 (1H, d, $J = 7.8$ Hz), 1.56 (3H, dd, $J = 7.1, 1.7$ Hz); ^{13}C NMR (75 MHz, CDCl_3) δ_{C} : 155.6, 134.6, 132.6, 132.4, 132.3, 130.1, 128.3, 122.7, 120.9, 61.5, 45.8, 14.8; MS (ESI:+ve) m/z : calcd for $\text{C}_{14}\text{H}_{15}\text{NO}_2\text{Cl}$: 264.0791 found: 264.0797 $[\text{M} + \text{H}]^+$

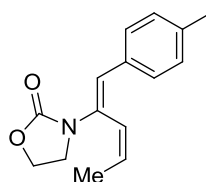
3-((1*E*,3*Z*)-1-(4-Nitrophenyl)penta-1,3-dien-2-yl)oxazolidin-2-one (359)

Prepared according to general procedure E using; ynamido ester **350** (100 μ g, 0.32 mmol, 1 equiv.), LiHMDS (1 M in THF, 573 μ L, 0.57 mmol, 1.8 equiv.), TMSCl (73 μ L, 0.57 mmol, 1.8 equiv.) and THF (2mL). Purification was achieved by flash chromatography to give diene **359** as a yellow oil (54 mg, 54 %, 2:1 *E/Z*).

FTIR (film/ cm^{-1}) ν_{max} : 2986, 2954, 2870, 1746, 1643, 1532; ^1H NMR (500 MHz, CDCl_3) δ_{H} : 8.06–8.02 (2H, m), 7.45–7.41 (2H, m), 6.58 (1H, s), 6.08–6.03 (1H, m), 5.87–5.79 (1H, m), 4.42–4.31 (2H, m), 3.85–3.77 (2H, m), 1.46 (3H, d, $J = 6.7$ Hz); ^{13}C

NMR (75 MHz, CDCl₃) δ_C 169.1, 155.8, 145.8, 135.7, 133.6, 129.9, 129.2, 123.6, 122.7, 69.8, 46.6, 18.4; MS (ESI:+ve) m/z : calcd for C₁₄H₁₄N₂O₄Na: 297.0852, found: 297.0863, [M + Na]⁺.

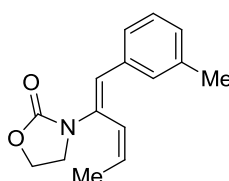
3-((1*E*,3*Z*)-1-(*p*-Tolyl)penta-1,3-dien-2-yl)oxazolidin-2-one (360)



Prepared according to general procedure E using; ynamido ester **287** (100 mg, 0.35 mmol, 1 equiv.), LiHMDS (1 M in THF, 633 μ L, 0.63 mmol, 1.8 equiv.), TMSCl (80 μ L, 0.63 mmol, 1.8 equiv.) and THF (2mL). Purification was achieved by flash chromatography to give diene **360** as a yellow oil (62 mg, 73 %, 3:1 *Z/E*).

FTIR (film/cm⁻¹) ν_{\max} : 3022, 2920, 1744, 1624; ¹H NMR (300 MHz, CDCl₃) δ_H (*Z* isomer): 7.26 (2H, app. d, J = 8.2 Hz), 7.09 (2H, app. d, J = 8.2 Hz), 6.53 (1H, app. s), 6.14–6.06 (1H, m), 5.87–5.74 (1H, m), 4.40 (1H, d, J = 7.7 Hz), 4.37 (1H, d, J = 6.7 Hz), 3.83 (1H, d J = 6.7 Hz), 3.80 (1H, d, J = 7.7 Hz), 2.33 (3H, s), 1.60 (3H, dd, J = 7.1, 1.9 Hz); δ_H (*E* isomer): 7.26 (2H, app. d, J = 8.2 Hz), 7.09 (2H, app. d, J = 8.2 Hz), 6.43 (1H, app. s), 6.29 (1H, app. d, J = 15.8 Hz), 5.92–5.74 (1H, m), 4.42–4.32 (2H, m), 3.83–3.73 (2H, m), 2.28 (3H, s), 1.77 (3H, dd, J = 6.7, 1.8 Hz); ¹³C NMR (75 MHz, CDCl₃) δ_C : 155.8, 136.8, 133.0, 131.4, 128.9, 128.8, 128.3, 123.3, 123.2, 61.6, 46.0, 21.2, 14.7; MS (ESI:+ve) m/z : calcd for C₁₅H₁₇NO₂Na: 266.1157, found: 266.1137, [M + Na]⁺

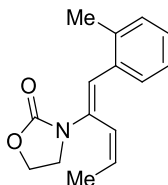
3-((1*E*,3*Z*)-1-(*m*-Tolyl)penta-1,3-dien-2-yl)oxazolidin-2-one (361)



Prepared according to general procedure E using; ynamido ester **351** (100 mg, 0.35 mmol, 1 equiv.), LiHMDS (1 M in THF, 631 μL , 0.63 mmol, 1.8 equiv.), TMSCl (80 μL , 0.63 mmol, 1.8 equiv.) and THF (2mL). Purification was achieved by flash chromatography to give diene **361** as a yellow oil (36 mg, 42 %, 6:1 *E/Z*).

FTIR (film/ cm^{-1}) ν_{max} : 2981, 2889, 1746, 1622; ^1H NMR (500 MHz, CDCl_3) δ_{H} (*Z* isomer): 7.21–7.13 (3H, m), 7.04–6.98 (1H, m), 6.52 (1H, app. s), 6.15–6.07 (1H, m), 5.81 (1H, dqd, $J = 11.5, 7.1, 0.6$ Hz), 4.41 (1H, d, $J = 7.9$ Hz), 4.38 (1H, d, $J = 6.6$ Hz), 3.83 (1H, d, $J = 6.6$ Hz), 3.80 (1H, d, $J = 7.9$ Hz), 2.32 (3H, s), 1.60 (3H, dd, $J = 7.1, 1.8$ Hz); δ_{H} (*E* isomer): 7.21–7.13 (3H, m), 7.04–6.98 (1H, m), 6.38 (1H, app. s), 6.23 (1H, app. d, $J = 16.5$ Hz), 5.86–5.72 (1H, m), 4.36–4.29 (2H, m), 3.76–3.70 (2H, m), 2.22 (3H, s), 1.73 (3H, dd, $J = 6.8, 1.6$ Hz); ^{13}C NMR (75 MHz, CDCl_3) δ_{C} : 155.8, 137.6, 135.8, 131.9, 131.5, 129.8, 128.0, 127.7, 126.0, 123.2, 123.2, 61.6, 46.0, 21.4, 14.8; MS (ESI:+ve) m/z : calcd for $\text{C}_{15}\text{H}_{17}\text{NO}_2\text{Na}$: 266.1157, found: 266.1143, $[\text{M} + \text{Na}]^+$

3-((1*E*,3*Z*)-1-(*o*-Tolyl)penta-1,3-dien-2-yl)oxazolidin-2-one (**362**)

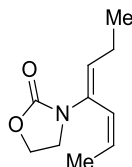


Prepared according to general procedure E using; ynamido ester **352** (100 mg, 0.35 mmol, 1 equiv.), LiHMDS (1 M in THF, 631 μL , 0.63 mmol, 1.8 equiv.), TMSCl (80 μL , 0.63 mmol, 1.8 equiv.) and THF (2mL). Purification was achieved by flash chromatography to give diene **362** as a yellow oil (37 mg, 43 %, 2:1 *E/Z*).

FTIR (film/ cm^{-1}) ν_{max} : 2998, 2890, 1753, 1621; ^1H NMR (500 MHz, CDCl_3) δ_{H} (*Z* isomer): 7.22–7.05 (4H, m), 6.59 (1H, app. s), 6.04–5.96 (1H, m), 5.75–5.62 (1H, m), 4.43 (1H, d, $J = 7.7$ Hz), 4.40 (1H, d, $J = 6.7$ Hz), 3.87 (1H, d, $J = 6.7$ Hz), 3.84 (1H, d, $J = 7.7$ Hz), 2.30 (3H, s), 1.47 (3H, dd, $J = 7.1, 1.8$ Hz); δ_{H} (*E* isomer): 7.22–7.05 (4H, m), 6.41 (1H, s), 6.01 (1H, dq, $J = 15.6, 1.6$ Hz), 5.74 (1H, dq, $J = 15.6, 6.6$ Hz), 4.37–4.29 (2H, m), 3.77–3.70 (2H, m), 2.13 (3H, s), 1.65 (3H, dd, $J = 6.6, 1.6$ Hz); ^{13}C NMR (75 MHz, CDCl_3) δ_{C} : 155.6, 139.2, 135.9, 133.6, 133.3, 129.2, 129.1, 128.8, 128.7, 124.4, 111.2,

61.4, 46.2, 22.1, 21.5; MS (ESI:+ve) m/z : calcd for $C_{15}H_{17}NO_2Na$: 266.1157, found: 266.1166, $[M + Na]^+$

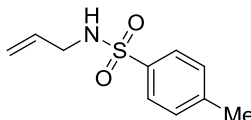
3-((2*E*,4*Z*)-Hepta-2,4-dien-4-yl)oxazolidin-2-one (363)



Prepared according to general procedure E using; ynamido ester **353** (100 mg, 0.44 mmol, 1 equiv.), LiHMDS (1 M in THF, 573 μ L, 0.57 mmol, 1.3 equiv.), TMSCl (72 μ L, 0.57 mmol, 1.3 equiv.) and THF (2mL). Purification was achieved by flash chromatography to give diene **363** as a yellow oil (23 mg, 32 %).

FTIR (film/ cm^{-1}) ν_{max} : 2963, 2935, 2876, 1748, 1643; 1H NMR (500 MHz, $CDCl_3$) δ_H : 5.82 (1H, d, $J = 11.4$ Hz), 5.72–5.68 (1H, m), 5.38 (1H, t, $J = 7.8$ Hz), 4.26–4.21 (2H, m), 3.64–3.60 (2H, m), 1.96 (2H, m), 1.58 (3H, dd, $J = 7.5, 1.5$ Hz), 0.92 (3H, t, $J = 7.8$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C : 156.2, 136.5, 130.4, 125.0, 122.7, 61.4, 46.0, 21.3, 14.8, 13.9; MS (ESI: +ve) m/z : calcd for $C_{10}H_{16}NO_2$: 182.1181, found: 182.1176, $[M + H]^+$.

N-Allyl-4-methylbenzenesulfonamide¹⁹⁴ (370)



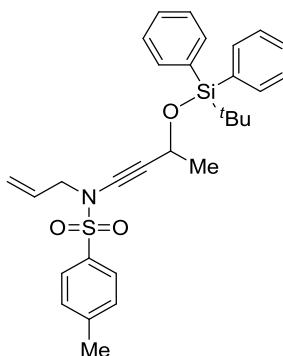
To a solution of allylamine (6.6 ml, 87.5 mmol) and triethylamine (11.0 ml, 79.6 mmol) in CH_2Cl_2 (250 mL) at reflux, was added slowly *p*-TsCl (15.2 g, 79.6 mmol). After 1 hour at reflux and 30 in at room temperature, the crude reaction mixture was added to a saturated aqueous solution of $NaHCO_3$ (120 mL). The product was extracted with CH_2Cl_2 (150 mL), washed with brine (2 x 100 mL) and dried over Na_2SO_4 , filtered and

evaporated in vacuo. The allyl sulfonamide was then recrystallised (CH₂Cl₂/Petroleum ether) affording clear crystals (16.0 g, 95 %).

¹H NMR (250 MHz, CDCl₃) δ_H: 7.69 (2H, app. d, *J* = 8.0 Hz), 7.25 (2H, app. d, *J* = 8.0 Hz), 5.65 (1H, ddt, *J* = 17.1, 10.2, 5.8 Hz), 5.10 (1H, dq, *J* = 17.1, 1.4 Hz), 5.04 (1H, dq, *J* = 10.2, 1.4 Hz), 4.34 (1H, brs), 3.52 (2H, tt, *J* = 5.8, 1.4 Hz), 2.37 (3H, s); ¹³C NMR (75 MHz, CDCl₃) δ_C: 143.9, 137.3, 133.4, 130.2, 127.6, 118.2, 46.2, 22.0.

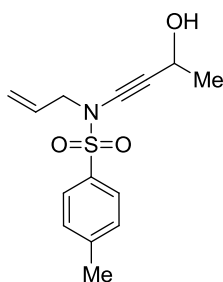
All other data in accordance with literature values.¹⁹⁴

***N*-Allyl-*N*-(3-(*tert*-butyldiphenylsilyloxy)but-1-ynyl)-4-methylbenzenesulfonamide (371)**



To a solution of bromo-alkyne **271** (5.0 g, 12.9 mmol, 1.1 equiv.) and *N*-allyl-4-methylbenzenesulfonamide (2.48 g, 11.8 mmol, 1 equiv.) in toluene (250 mL) was added CuSO₄·5H₂O (586 mg, 2.36 mmol, 20 mol%), 1,10-phenanthroline (847 mg, 4.72 mmol, 40 mol%) and K₃PO₄ (4.99 g, 23.5 mmol, 2 equiv.). The suspension was heated to 65 °C and stirred for 48 h, filtered through celite and concentrated *in vacuo*. Purification via flash chromatography, eluting with 8:1 Pet/EtOAc, afforded ynamide **371** as a yellow oil (4.70g, 78%).

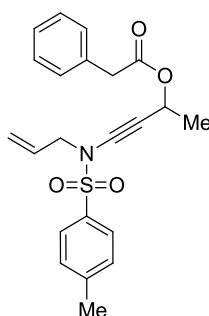
¹H NMR (250 MHz, CDCl₃) δ_H: 7.70–7.56 (4H, m), 7.36–7.17 (10H, m), 5.53 (1H, m), 5.05 (2H, m), 4.53 (1H, q, *J* = 6.5 Hz), 3.74 (2H, m), 2.36 (3H, s), 1.32 (3H, d, *J* = 6.5 Hz), 0.97 (9H, s); ¹³C NMR (75 MHz, CDCl₃) δ_C: 144.8, 136.3, 136.1, 135.6, 135.2, 134.2, 131.4, 130.0, 129.9, 128.1, 128.0, 127.8, 120.0, 77.6, 73.6, 60.6, 54.5, 27.2, 25.7, 22.0, 19.6.

***N*-Allyl-*N*-(3-hydroxybut-1-ynyl)-4-methylbenzenesulfonamide (372)**

To a solution of the protected ynamide **371** (5.0g, 9.7 mmol, 1 equiv.) in THF (200 mL) was added TBAF (1M in THF, 19 mL, 19.3 mmol, 2 equiv.) at 0 °C. The resultant solution was then warmed to rt, after 40 min the reaction mixture was hydrolysed with NH₄Cl (sat) (25 mL) and extracted with EtOAc (3 x 25 mL). The combined extracts were dried over MgSO₄, filtered and concentrated *in vacuo*. The crude material was purified by rapid filtration through silica gel (EtOAc) to give alcohol **372** as a clear oil (1.78 g, 70%).

¹H NMR (250 MHz, CDCl₃) δ_H 7.78–7.70 (2H, m), 7.31–7.26 (2H, m), 5.68–5.59 (1H, m), 5.19–5.11 (2H, m), 4.56 (1H, q, *J* = 6.4 Hz), 3.90–3.83 (2H, m), 2.38 (3H, s), 1.96 (1H, brs), 1.36 (3H, d, *J* = 6.5 Hz); ¹³C NMR (75 MHz, CDCl₃) δ_C 145.1, 135.0, 131.2, 130.1, 128.1, 120.4, 77.6, 73.5, 58.9, 54.5, 24.8, 22.0.

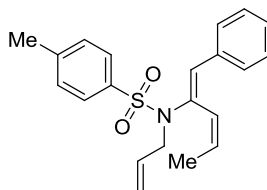
All other data in accordance with literature precedence.¹⁸¹

4-(*N*-Allyl-4-methylphenylsulfonamido)but-3-yn-2-yl 2-phenylacetate (373)

Prepared according to general procedure C using; propargyl alcohol **372** (1.66 g, 5.96 mmol, 1 equiv.), phenylacetic acid (1.62 g, 11.9 mmol, 2 equiv.), EDCi (2.3 g, 11.9 mmol, 2 equiv.), triethylamine (1.7 mL, 11.9 mmol, 2 equiv.), DMAP (147 mg, 1.2 mmol, 20 mol%) and DCM (100 mL). Purification was achieved by flash chromatography yielding ester **373** as a yellow solid (1.92 g, 81%).

FTIR (film/cm⁻¹) ν_{\max} : 3032, 2986, 2934, 2247, 1735 1597; ¹H NMR (250 MHz, CDCl₃) δ_{H} 7.73–7.66 (2H, m), 7.28–7.13 (7H, m), 5.60 (1H, m), 5.47 (1H, q, $J = 6.7$), 5.14–5.09 (2H, m), 3.88–3.82 (2H, m), 3.53 (2H, s), 2.37 (3H, s), 1.39 (3H, d, $J = 6.7$ Hz); ¹³C NMR (75 MHz, CDCl₃) δ_{C} 170.8, 145.1, 135.0, 134.2, 131.0, 130.1, 129.9, 129.6, 129.1, 128.9, 128.2, 127.5, 120.5, 78.88, 77.65, 70.5, 61.6, 54.5, 49.5, 41.6, 22.1, 21.7; MS (ESI:+ve) m/z : calcd for C₂₂H₂₄NO₄S: 398.1426, found 398.1417 [M + H]⁺

N-Allyl-4-methyl-N-((1E,3Z)-1-phenylpenta-1,3-dien-2-yl)benzenesulfonamide (374)



Prepared according to general procedure E using; ynamido ester **373** (0.10 g, 0.25 mmol, 1 equiv.), LiHMDS (1 M in THF, 0.33 mL, 0.33 mmol, 1.3 equiv.), TMSCl (41 μ L, 0.33 mmol, 1.3 equiv.) and THF (2mL). Purification was achieved by flash chromatography to give diene **374** as a yellow oil (8 mg, 9 %).

FTIR (film/cm⁻¹) ν_{\max} : 2937, 2917, 1734, 1597; ¹H NMR (500 MHz, CDCl₃) δ_{H} 7.78–7.74 (2H, m), 7.36–7.25 (7H, m), 6.50 (1H, s), 6.36 (1H, app. d, $J = 15.2$ Hz), 6.10 (1H, dq, $J = 15.2, 7.1$ Hz), 5.63–5.57 (1H, m), 5.12–5.07 (2H, m), 3.97–3.92 (2H, m), 2.19 (3H, s), 1.28 (3H, t, $J = 7.1$ Hz); ¹³C NMR (75 MHz, CDCl₃) δ_{C} 143.4, 137.3, 134.7, 133.0, 131.5, 131.1, 129.7, 129.5, 129.2, 129.1, 128.8, 128.5, 118.4, 110.2, 49.1, 20.5, 19.5. MS (ESI: +ve) m/z : calcd for C₂₁H₂₄NO₂S: 354.1528, found: 354.1519, [M + H]⁺.

6. APPENDIX

6.1 Crystal data for 206

Table 1. Crystal data and structure refinement for **206**.

Identification code	k11dc1
Empirical formula	C ₂₂ H _{20.83} N _{1.17} O _{1.33}
Formula weight	322.91
Temperature	150(2) K
Wavelength	0.71073 Å
Crystal system	Trigonal
Space group	R-3
Unit cell dimensions	a = 22.3950(6) Å alpha = 90° b = 22.3950(6) Å beta = 90° c = 22.7710(8) Å gamma = 120°
Volume	9890.4(5) Å ³
Z	18
Density (calculated)	0.976 Mg/m ³
Absorption coefficient	0.060 mm ⁻¹
F(000)	3090
Crystal size	0.50 x 0.40 x 0.13 mm
Theta range for data collection	3.73 to 24.87°
Index ranges	-26 ≤ h ≤ 26; -26 ≤ k ≤ 25; -26 ≤ l ≤ 26
Reflections collected	51664
Independent reflections	3812 [R(int) = 0.1439]
Reflections observed (>2σ)	3063
Data Completeness	0.996
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.232 and 0.473
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	3812 / 0 / 213
Goodness-of-fit on F ²	1.107
Final R indices [I>2σ(I)]	R1 = 0.1333 wR2 = 0.3400
R indices (all data)	R1 = 0.1570 wR2 = 0.3587
Largest diff. peak and hole	0.310 and -0.295 eÅ ⁻³

Notes:

The crystals were visually beautiful for this sample – so it was quite a surprise to see minimal diffraction intensity beyond a Bragg angle of approximately 21°. Thus, in the refinement, data were truncated to a max theta value of 25°. The larger than desirable R_{int} value purely reflects this facet of the data set.

The reason for this diffraction fall-off became obvious when the structure was solved and refined. Analysis revealed that almost 33% of the unit cell volume is composed of a diffuse/disordered solvent, which did not lend itself to modelling.

Thus, PLATON SQUEEZE was employed to estimate the contribution of the latter to diffraction and to generate a data set of solvent-free diffraction intensities. SQUEEZE suggested a total count of 207 electrons in accessible unit cell ‘voids’, which were assigned as 3 molecules of acetonitrile plus 3 molecules of ethyl acetate per unit cell. The final formula presented herein includes this level of solvent.

Intermolecular N-H...O bonds serve to generate hydrogen-bonded chains along *c* in the gross structure.

Table 2. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for **206**. U(equiv.) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

Atom	x	y	z	U(equiv.)
O(1)	782(2)	3929(2)	-1068(2)	132(2)
N(1)	285(2)	2534(2)	1134(1)	63(1)
C(1)	427(2)	2012(2)	1158(2)	63(1)
C(2)	328(2)	1545(2)	1620(2)	69(1)
C(3)	549(3)	1090(3)	1532(2)	78(1)
C(4)	850(3)	1052(3)	995(2)	85(1)
C(5)	944(2)	1503(3)	551(2)	74(1)
C(6)	745(2)	1999(2)	631(2)	64(1)
C(7)	777(2)	2539(2)	277(2)	68(1)
C(8)	1077(2)	2710(3)	-335(2)	81(2)
C(9)	595(3)	2843(3)	-753(2)	92(2)
C(10)	643(3)	3538(3)	-646(3)	97(2)
C(11)	529(3)	3747(3)	-89(2)	90(2)
C(12)	444(2)	3475(3)	464(2)	81(1)
C(13)	502(2)	2867(2)	596(2)	66(1)
C(14)	1822(3)	3327(3)	-333(2)	99(2)
C(15)	704(4)	2712(4)	-1394(2)	131(3)
C(16)	325(3)	3847(3)	960(2)	86(2)
C(17)	-168(3)	4061(4)	888(3)	114(2)
C(18)	-259(4)	4427(4)	1340(4)	133(3)
C(19)	83(4)	4557(4)	1858(4)	123(2)
C(20)	558(4)	4342(3)	1926(3)	108(2)
C(21)	677(3)	3988(3)	1478(2)	87(2)

Table 3. Bond lengths [Å] and angles [°] for **206**.

O(1)-C(10)	1.231(6)	N(1)-C(1)	1.359(6)
N(1)-C(13)	1.389(5)	N(1)-H(1)	0.8800
C(1)-C(6)	1.402(6)	C(1)-C(2)	1.419(6)
C(2)-C(3)	1.351(7)	C(2)-H(2)	0.9500
C(3)-C(4)	1.419(7)	C(3)-H(3)	0.9500
C(4)-C(5)	1.367(7)	C(4)-H(4)	0.9500
C(5)-C(6)	1.401(6)	C(5)-H(5)	0.9500
C(6)-C(7)	1.425(6)	C(7)-C(13)	1.377(6)
C(7)-C(8)	1.512(6)	C(8)-C(14)	1.546(7)
C(8)-C(9)	1.575(7)	C(8)-H(8)	1.0000
C(9)-C(10)	1.523(9)	C(9)-C(15)	1.535(7)
C(9)-H(9)	1.0000	C(10)-C(11)	1.421(8)
C(11)-C(12)	1.370(7)	C(11)-H(11)	0.9500
C(12)-C(13)	1.463(7)	C(12)-C(16)	1.504(7)
C(14)-H(14A)	0.9800	C(14)-H(14B)	0.9800
C(14)-H(14C)	0.9800	C(15)-H(15A)	0.9800
C(15)-H(15B)	0.9800	C(15)-H(15C)	0.9800
C(16)-C(21)	1.366(8)	C(16)-C(17)	1.415(8)
C(17)-C(18)	1.394(10)	C(17)-H(17)	0.9500
C(18)-C(19)	1.355(10)	C(18)-H(18)	0.9500
C(19)-C(20)	1.378(10)	C(19)-H(19)	0.9500
C(20)-C(21)	1.396(8)	C(20)-H(20)	0.9500
C(21)-H(21)	0.9500		
C(1)-N(1)-C(13)	109.1(3)	C(1)-N(1)-H(1)	125.4
C(13)-N(1)-H(1)	125.4	N(1)-C(1)-C(6)	108.8(4)
N(1)-C(1)-C(2)	130.3(4)	C(6)-C(1)-C(2)	120.8(4)
C(3)-C(2)-C(1)	117.7(4)	C(3)-C(2)-H(2)	121.2
C(1)-C(2)-H(2)	121.2	C(2)-C(3)-C(4)	122.4(4)
C(2)-C(3)-H(3)	118.8	C(4)-C(3)-H(3)	118.8
C(5)-C(4)-C(3)	119.7(5)	C(5)-C(4)-H(4)	120.2
C(3)-C(4)-H(4)	120.2	C(4)-C(5)-C(6)	119.8(4)
C(4)-C(5)-H(5)	120.1	C(6)-C(5)-H(5)	120.1
C(5)-C(6)-C(1)	119.6(4)	C(5)-C(6)-C(7)	134.3(4)
C(1)-C(6)-C(7)	106.1(4)	C(13)-C(7)-C(6)	107.9(3)
C(13)-C(7)-C(8)	127.7(4)	C(6)-C(7)-C(8)	124.4(4)
C(7)-C(8)-C(14)	111.5(4)	C(7)-C(8)-C(9)	110.2(4)
C(14)-C(8)-C(9)	111.7(4)	C(7)-C(8)-H(8)	107.8
C(14)-C(8)-H(8)	107.8	C(9)-C(8)-H(8)	107.8
C(10)-C(9)-C(15)	114.3(5)	C(10)-C(9)-C(8)	113.1(4)
C(15)-C(9)-C(8)	110.3(5)	C(10)-C(9)-H(9)	106.2
C(15)-C(9)-H(9)	106.2	C(8)-C(9)-H(9)	106.2
O(1)-C(10)-C(11)	119.0(6)	O(1)-C(10)-C(9)	117.9(6)
C(11)-C(10)-C(9)	123.1(5)	C(12)-C(11)-C(10)	133.0(6)
C(12)-C(11)-H(11)	113.5	C(10)-C(11)-H(11)	113.5
C(11)-C(12)-C(13)	123.1(5)	C(11)-C(12)-C(16)	117.8(5)
C(13)-C(12)-C(16)	119.0(4)	C(7)-C(13)-N(1)	108.0(4)
C(7)-C(13)-C(12)	131.3(4)	N(1)-C(13)-C(12)	120.7(4)

C(8)-C(14)-H(14A)	109.5	C(8)-C(14)-H(14B)	109.5
H(14A)-C(14)-H(14B)	109.5	C(8)-C(14)-H(14C)	109.5
H(14A)-C(14)-H(14C)	109.5	H(14B)-C(14)-H(14C)	109.5
C(9)-C(15)-H(15A)	109.5	C(9)-C(15)-H(15B)	109.5
H(15A)-C(15)-H(15B)	109.5	C(9)-C(15)-H(15C)	109.5
H(15A)-C(15)-H(15C)	109.5	H(15B)-C(15)-H(15C)	109.5
C(21)-C(16)-C(17)	118.6(6)	C(21)-C(16)-C(12)	122.3(5)
C(17)-C(16)-C(12)	119.1(6)	C(18)-C(17)-C(16)	118.8(7)
C(18)-C(17)-H(17)	120.6	C(16)-C(17)-H(17)	120.6
C(19)-C(18)-C(17)	122.3(7)	C(19)-C(18)-H(18)	118.8
C(17)-C(18)-H(18)	118.8	C(18)-C(19)-C(20)	118.4(7)
C(18)-C(19)-H(19)	120.8	C(20)-C(19)-H(19)	120.8
C(19)-C(20)-C(21)	121.1(7)	C(19)-C(20)-H(20)	119.5
C(21)-C(20)-H(20)	119.5	C(16)-C(21)-C(20)	120.7(6)
C(16)-C(21)-H(21)	119.7	C(20)-C(21)-H(21)	119.7

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for **206**. The anisotropic displacement factor exponent takes the form: $-2 \text{ gpi}^2 [h^2 a^{*2} U_{11} + \dots + 2 h k a^* b^* U_{12}]$

Atom	U11	U22	U33	U23	U13	U12
O(1)	129(3)	133(3)	78(3)	52(2)	-13(2)	23(3)
N(1)	63(2)	84(2)	47(2)	3(2)	11(2)	40(2)
C(1)	56(2)	79(3)	47(2)	-8(2)	-5(2)	28(2)
C(2)	71(3)	76(3)	45(2)	1(2)	3(2)	26(2)
C(3)	90(3)	73(3)	63(3)	6(2)	-7(2)	36(3)
C(4)	98(4)	87(3)	76(3)	-1(3)	5(3)	52(3)
C(5)	76(3)	91(3)	54(2)	-9(2)	3(2)	41(3)
C(6)	62(2)	84(3)	43(2)	-4(2)	-1(2)	33(2)
C(7)	56(2)	95(3)	43(2)	7(2)	-1(2)	30(2)
C(8)	77(3)	112(4)	46(2)	7(2)	11(2)	41(3)
C(9)	75(3)	133(5)	40(2)	7(3)	-4(2)	30(3)
C(10)	81(3)	100(4)	79(4)	28(3)	-7(3)	21(3)
C(11)	74(3)	114(4)	79(3)	25(3)	5(2)	45(3)
C(12)	62(3)	98(4)	77(3)	22(3)	5(2)	36(3)
C(13)	58(2)	91(3)	51(2)	11(2)	6(2)	38(2)
C(14)	72(3)	153(5)	56(3)	18(3)	12(2)	45(3)
C(15)	114(5)	189(7)	44(3)	26(3)	5(3)	42(5)
C(16)	81(3)	100(4)	89(4)	18(3)	23(3)	55(3)
C(17)	96(4)	146(6)	116(5)	26(4)	13(4)	72(4)
C(18)	141(6)	155(7)	153(7)	5(6)	44(6)	112(6)
C(19)	149(6)	119(5)	119(6)	10(4)	40(5)	80(5)
C(20)	123(5)	102(4)	108(5)	-7(3)	14(4)	63(4)

C(21)	88(3)	88(3)	87(4)	6(3)	9(3)	46(3)
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Table 5. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for **206**.

Atom	x	y	z	U(equiv.)
H(1)	86	2643	1414	69(12)
H(2)	114	1552	1978	82
H(3)	501	784	1841	93
H(4)	985	715	944	102
H(5)	1144	1479	190	89
H(8)	1092	2299	-489	57(11)
H(9)	111	2485	-651	79(13)
H(11)	508	4160	-102	108
H(14A)	1822	3738	-186	148
H(14B)	2008	3412	-733	148
H(14C)	2110	3222	-77	148
H(15A)	341	2704	-1639	196
H(15B)	687	2267	-1424	196
H(15C)	1155	3080	-1529	196
H(17)	-431	3958	537	137
H(18)	-572	4592	1284	159
H(19)	-3	4790	2166	148
H(20)	808	4436	2283	130
H(21)	1006	3844	1535	104

Table 6. Dihedral angles [$^{\circ}$] for **206**.

Atom1 - Atom2 - Atom3 - Atom4	Dihedral
C(13) - N(1) - C(1) - C(6)	0.1(5)
C(13) - N(1) - C(1) - C(2)	177.4(4)
N(1) - C(1) - C(2) - C(3)	-177.1(4)
C(6) - C(1) - C(2) - C(3)	-0.1(6)
C(1) - C(2) - C(3) - C(4)	-2.1(7)
C(2) - C(3) - C(4) - C(5)	2.1(8)
C(3) - C(4) - C(5) - C(6)	0.2(7)
C(4) - C(5) - C(6) - C(1)	-2.3(7)
C(4) - C(5) - C(6) - C(7)	178.8(5)
N(1) - C(1) - C(6) - C(5)	179.8(4)
C(2) - C(1) - C(6) - C(5)	2.3(6)
N(1) - C(1) - C(6) - C(7)	-1.0(4)
C(2) - C(1) - C(6) - C(7)	-178.5(4)
C(5) - C(6) - C(7) - C(13)	-179.5(5)
C(1) - C(6) - C(7) - C(13)	1.5(5)
C(5) - C(6) - C(7) - C(8)	-0.4(8)
C(1) - C(6) - C(7) - C(8)	-179.4(4)
C(13) - C(7) - C(8) - C(14)	79.7(6)
C(6) - C(7) - C(8) - C(14)	-99.2(6)
C(13) - C(7) - C(8) - C(9)	-44.9(7)
C(6) - C(7) - C(8) - C(9)	136.2(5)
C(7) - C(8) - C(9) - C(10)	74.7(6)
C(14) - C(8) - C(9) - C(10)	-49.8(6)
C(7) - C(8) - C(9) - C(15)	-155.9(5)
C(14) - C(8) - C(9) - C(15)	79.6(6)
C(15) - C(9) - C(10) - O(1)	-2.1(7)
C(8) - C(9) - C(10) - O(1)	125.2(5)
C(15) - C(9) - C(10) - C(11)	177.3(5)
C(8) - C(9) - C(10) - C(11)	-55.3(7)
O(1) - C(10) - C(11) - C(12)	-171.5(6)
C(9) - C(10) - C(11) - C(12)	9.0(9)
C(10) - C(11) - C(12) - C(13)	4.1(9)
C(10) - C(11) - C(12) - C(16)	-179.3(5)
C(6) - C(7) - C(13) - N(1)	-1.4(5)
C(8) - C(7) - C(13) - N(1)	179.5(4)
C(6) - C(7) - C(13) - C(12)	175.8(5)
C(8) - C(7) - C(13) - C(12)	-3.3(8)
C(1) - N(1) - C(13) - C(7)	0.8(5)
C(1) - N(1) - C(13) - C(12)	-176.7(4)
C(11) - C(12) - C(13) - C(7)	15.5(8)
C(16) - C(12) - C(13) - C(7)	-161.0(5)
C(11) - C(12) - C(13) - N(1)	-167.6(4)
C(16) - C(12) - C(13) - N(1)	15.9(6)
C(11) - C(12) - C(16) - C(21)	-132.6(5)

C(13) - C(12) - C(16) - C(21)	44.1(7)
C(11) - C(12) - C(16) - C(17)	47.1(7)
C(13) - C(12) - C(16) - C(17)	-136.1(5)
C(21) - C(16) - C(17) - C(18)	2.0(9)
C(12) - C(16) - C(17) - C(18)	-177.8(6)
C(16) - C(17) - C(18) - C(19)	-3.2(12)
C(17) - C(18) - C(19) - C(20)	2.8(12)
C(18) - C(19) - C(20) - C(21)	-1.2(11)
C(17) - C(16) - C(21) - C(20)	-0.5(8)
C(12) - C(16) - C(21) - C(20)	179.2(5)
C(19) - C(20) - C(21) - C(16)	0.1(9)

Symmetry transformations used to generate equivalent atoms:

6.2 Crystal data for 282

Table 1. Crystal data and structure refinement for **282**.

Identification code	k11dc3a
Empirical formula	C ₂₃ H ₂₁ I N ₂ O ₄
Formula weight	516.32
Temperature	298(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	Pbca
Unit cell dimensions	a = 9.4740(1) Å alpha = 90° b = 21.0690(2) Å beta = 90° c = 22.6350(2) Å gamma = 90°
Volume	4518.12(8) Å ³
Z	298
Density (calculated)	1.518 Mg/m ³
Absorption coefficient	1.448 mm ⁻¹
F(000)	2064
Crystal size	0.45 x 0.30 x 0.10 mm
Theta range for data collection	3.58 to 25.03°
Index ranges	-11 ≤ h ≤ 11; -25 ≤ k ≤ 24; -26 ≤ l ≤ 26
Reflections collected	65108
Independent reflections	3968 [R(int) = 0.0493]
Reflections observed (>2sigma)	3224
Data Completeness	0.993
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.662 and 0.526
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	3968 / 0 / 272
Goodness-of-fit on F ²	1.087
Final R indices [I>2sigma(I)]	R1 = 0.0768 wR2 = 0.2015
R indices (all data)	R1 = 0.0895 wR2 = 0.2137
Largest diff. peak and hole	2.229 and -2.162 eÅ ⁻³

Notes:

Incomplete phase transition upon cooling to 150 K. thus, structure completed at 298 K.

H-bonding in lattice.

Hydrogen bonds with $H..A < r(A) + 2.000$ Angstroms and $\angle DHA > 110^\circ$.

D-H d(D-H) d(H..A) $\angle DHA$ d(D..A) A

N1-H1 0.880 2.047 157.73 2.881 O4 [-x+1/2, y-1/2, z]

Table 2. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for **282**. U(equiv.) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

Atom	x	y	z	U(equiv.)
I(1)	-228(1)	2961(1)	285(1)	119(1)
O(1)	4507(4)	3488(2)	1500(2)	60(1)
O(2)	6714(5)	3857(3)	1538(2)	97(2)
O(3)	4381(7)	4690(2)	2924(2)	92(2)
O(4)	3637(8)	4594(2)	2004(3)	120(2)
N(1)	2296(8)	889(2)	1892(3)	90(2)
N(2)	4586(5)	3744(2)	2507(2)	54(1)
C(1)	561(7)	2262(3)	862(3)	72(2)
C(2)	-311(8)	1764(5)	1006(4)	93(2)
C(3)	145(9)	1286(4)	1365(4)	95(3)
C(4)	1528(8)	1309(3)	1568(3)	72(2)
C(5)	2418(6)	1830(2)	1444(2)	54(1)
C(6)	1911(6)	2317(3)	1085(2)	58(1)
C(7)	3758(6)	1708(2)	1716(2)	56(1)
C(8)	3629(9)	1121(3)	1975(3)	76(2)
C(9)	4994(6)	2156(3)	1718(3)	59(1)
C(10)	6400(8)	1823(4)	1823(4)	95(2)
C(11)	4779(6)	2654(3)	2184(2)	54(1)
C(12)	4634(5)	3270(2)	2079(2)	50(1)
C(13)	5649(8)	3798(3)	1273(3)	71(2)
C(14)	5303(9)	4022(4)	658(3)	96(3)
C(15)	6418(8)	4424(3)	380(3)	71(2)
C(16)	7094(8)	4243(4)	-124(3)	82(2)
C(17)	8060(10)	4635(5)	-389(3)	102(3)
C(18)	8342(10)	5217(5)	-158(4)	99(2)
C(19)	7728(13)	5400(4)	341(5)	126(4)
C(20)	6782(12)	4999(4)	619(4)	126(4)
C(21)	4152(9)	4354(3)	2433(3)	77(2)
C(22)	5095(8)	3630(3)	3101(3)	79(2)
C(23)	4993(9)	4291(4)	3370(3)	86(2)

Table 3. Bond lengths [Å] and angles [°] for **282**.

I(1)-C(1)	2.108(7)	O(1)-C(13)	1.364(7)
O(1)-C(12)	1.394(6)	O(2)-C(13)	1.180(8)
O(3)-C(21)	1.335(8)	O(3)-C(23)	1.435(9)
O(4)-C(21)	1.197(8)	N(1)-C(4)	1.360(9)
N(1)-C(8)	1.367(10)	N(1)-H(1)	0.8800
N(2)-C(21)	1.360(7)	N(2)-C(12)	1.394(7)
N(2)-C(22)	1.448(8)	C(1)-C(2)	1.375(11)
C(1)-C(6)	1.380(9)	C(2)-C(3)	1.363(13)
C(2)-H(2)	0.9500	C(3)-C(4)	1.390(11)
C(3)-H(3)	0.9500	C(4)-C(5)	1.412(8)
C(5)-C(6)	1.393(8)	C(5)-C(7)	1.434(8)
C(6)-H(6)	0.9500	C(7)-C(8)	1.372(8)
C(7)-C(9)	1.505(8)	C(8)-H(8)	0.9500
C(9)-C(11)	1.500(8)	C(9)-C(10)	1.525(9)
C(9)-H(9)	1.0000	C(10)-H(10A)	0.9800
C(10)-H(10B)	0.9800	C(10)-H(10C)	0.9800
C(11)-C(12)	1.326(8)	C(11)-H(11)	0.9500
C(13)-C(14)	1.506(9)	C(14)-C(15)	1.494(10)
C(14)-H(14A)	0.9900	C(14)-H(14B)	0.9900
C(15)-C(16)	1.361(9)	C(15)-C(20)	1.371(11)
C(16)-C(17)	1.372(11)	C(16)-H(16)	0.9500
C(17)-C(18)	1.360(12)	C(17)-H(17)	0.9500
C(18)-C(19)	1.326(12)	C(18)-H(18)	0.9500
C(19)-C(20)	1.383(12)	C(19)-H(19)	0.9500
C(20)-H(20)	0.9500	C(22)-C(23)	1.523(10)
C(22)-H(22A)	0.9900	C(22)-H(22B)	0.9900
C(23)-H(23A)	0.9900	C(23)-H(23B)	0.9900
C(13)-O(1)-C(12)	116.2(4)	C(21)-O(3)-C(23)	110.0(5)
C(4)-N(1)-C(8)	109.6(5)	C(4)-N(1)-H(1)	125.2
C(8)-N(1)-H(1)	125.2	C(21)-N(2)-C(12)	127.0(5)
C(21)-N(2)-C(22)	111.8(5)	C(12)-N(2)-C(22)	121.1(5)
C(2)-C(1)-C(6)	122.3(7)	C(2)-C(1)-I(1)	117.9(6)
C(6)-C(1)-I(1)	119.8(5)	C(3)-C(2)-C(1)	120.9(7)
C(3)-C(2)-H(2)	119.5	C(1)-C(2)-H(2)	119.5
C(2)-C(3)-C(4)	118.1(7)	C(2)-C(3)-H(3)	121.0
C(4)-C(3)-H(3)	121.0	N(1)-C(4)-C(3)	131.3(7)
N(1)-C(4)-C(5)	107.1(6)	C(3)-C(4)-C(5)	121.6(7)
C(6)-C(5)-C(4)	118.8(6)	C(6)-C(5)-C(7)	133.5(5)
C(4)-C(5)-C(7)	107.6(5)	C(1)-C(6)-C(5)	118.1(6)
C(1)-C(6)-H(6)	121.0	C(5)-C(6)-H(6)	121.0
C(8)-C(7)-C(9)	105.5(6)	C(8)-C(7)-C(9)	129.2(6)
C(5)-C(7)-C(9)	125.3(5)	N(1)-C(8)-C(7)	110.2(6)
N(1)-C(8)-H(8)	124.9	C(7)-C(8)-H(8)	124.9
C(11)-C(9)-C(7)	109.6(5)	C(11)-C(9)-C(10)	109.4(5)
C(7)-C(9)-C(10)	113.0(6)	C(11)-C(9)-H(9)	108.2
C(7)-C(9)-H(9)	108.2	C(10)-C(9)-H(9)	108.2
C(9)-C(10)-H(10A)	109.5	C(9)-C(10)-H(10B)	109.5

H(10A)-C(10)-H(10B)	109.5	C(9)-C(10)-H(10C)	109.5
H(10A)-C(10)-H(10C)	109.5	H(10B)-C(10)-H(10C)	109.5
C(12)-C(11)-C(9)	124.9(5)	C(12)-C(11)-H(11)	117.5
C(9)-C(11)-H(11)	117.5	C(11)-C(12)-N(2)	125.5(5)
C(11)-C(12)-O(1)	120.0(5)	N(2)-C(12)-O(1)	114.5(4)
O(2)-C(13)-O(1)	122.5(5)	O(2)-C(13)-C(14)	128.5(6)
O(1)-C(13)-C(14)	108.9(6)	C(15)-C(14)-C(13)	114.5(6)
C(15)-C(14)-H(14A)	108.6	C(13)-C(14)-H(14A)	108.6
C(15)-C(14)-H(14B)	108.6	C(13)-C(14)-H(14B)	108.6
H(14A)-C(14)-H(14B)	107.6	C(16)-C(15)-C(20)	117.4(7)
C(16)-C(15)-C(14)	121.8(7)	C(20)-C(15)-C(14)	120.8(7)
C(15)-C(16)-C(17)	120.8(7)	C(15)-C(16)-H(16)	119.6
C(17)-C(16)-H(16)	119.6	C(18)-C(17)-C(16)	120.3(8)
C(18)-C(17)-H(17)	119.8	C(16)-C(17)-H(17)	119.8
C(19)-C(18)-C(17)	120.3(8)	C(19)-C(18)-H(18)	119.9
C(17)-C(18)-H(18)	119.9	C(18)-C(19)-C(20)	119.6(8)
C(18)-C(19)-H(19)	120.2	C(20)-C(19)-H(19)	120.2
C(15)-C(20)-C(19)	121.5(8)	C(15)-C(20)-H(20)	119.2
C(19)-C(20)-H(20)	119.2	O(4)-C(21)-O(3)	121.2(6)
O(4)-C(21)-N(2)	128.4(6)	O(3)-C(21)-N(2)	110.4(6)
N(2)-C(22)-C(23)	101.4(5)	N(2)-C(22)-H(22A)	111.5
C(23)-C(22)-H(22A)	111.5	N(2)-C(22)-H(22B)	111.5
C(23)-C(22)-H(22B)	111.5	H(22A)-C(22)-H(22B)	109.3
O(3)-C(23)-C(22)	106.2(5)	O(3)-C(23)-H(23A)	110.5
C(22)-C(23)-H(23A)	110.5	O(3)-C(23)-H(23B)	110.5
C(22)-C(23)-H(23B)	110.5	H(23A)-C(23)-H(23B)	108.7

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for **282**. The anisotropic displacement factor exponent takes the form: $-2 \pi^2 [h^2 a^{*2} U_{11} + \dots + 2 h k a^* b^* U_{12}]$

Atom	U11	U22	U33	U23	U13	U12
I(1)	127(1)	119(1)	110(1)	-18(1)	-50(1)	37(1)
O(1)	65(2)	62(2)	53(2)	10(2)	-10(2)	-8(2)
O(2)	70(3)	140(5)	82(3)	38(3)	-11(3)	-32(3)
O(3)	134(4)	49(2)	93(3)	-10(2)	-9(3)	-8(3)
O(4)	205(7)	58(3)	98(4)	7(3)	-33(4)	47(4)
N(1)	143(6)	45(3)	81(4)	1(3)	14(4)	-26(3)
N(2)	61(3)	47(2)	53(2)	5(2)	-7(2)	-3(2)
C(1)	65(4)	74(4)	76(4)	-21(3)	-1(3)	2(3)
C(2)	68(4)	123(7)	88(5)	-32(5)	4(4)	-16(5)
C(3)	96(6)	96(6)	92(5)	-23(5)	21(5)	-53(5)
C(4)	95(5)	56(3)	64(4)	-9(3)	15(3)	-19(3)
C(5)	65(3)	42(2)	55(3)	-9(2)	11(3)	-7(2)
C(6)	61(3)	50(3)	62(3)	-10(2)	2(3)	1(2)
C(7)	76(4)	38(3)	55(3)	-3(2)	7(3)	5(2)
C(8)	120(6)	47(3)	63(4)	5(3)	5(4)	11(4)
C(9)	59(3)	61(3)	57(3)	-2(3)	3(3)	4(3)
C(10)	75(5)	108(6)	102(5)	-24(5)	-2(4)	33(4)
C(11)	61(3)	49(3)	51(3)	4(2)	2(2)	2(2)
C(12)	48(3)	53(3)	48(3)	5(2)	-3(2)	-7(2)
C(13)	74(4)	83(4)	56(3)	15(3)	3(3)	-14(3)
C(14)	112(6)	113(6)	64(4)	27(4)	-10(4)	-30(5)
C(15)	86(4)	71(4)	57(3)	13(3)	3(3)	3(3)
C(16)	94(5)	93(5)	59(4)	-5(3)	-11(4)	-8(4)
C(17)	93(5)	145(8)	68(4)	-16(5)	16(4)	-23(5)
C(18)	102(6)	113(6)	82(5)	25(5)	4(5)	-20(5)
C(19)	184(11)	58(4)	135(8)	-8(5)	51(7)	-10(6)
C(20)	177(10)	83(5)	118(7)	-17(5)	78(7)	-10(6)
C(21)	101(5)	50(3)	79(4)	-1(3)	-7(4)	3(3)
C(22)	104(5)	74(4)	59(4)	-2(3)	-20(3)	10(4)
C(23)	99(5)	82(5)	76(4)	-17(4)	-10(4)	-15(4)

Table 5. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for **282**.

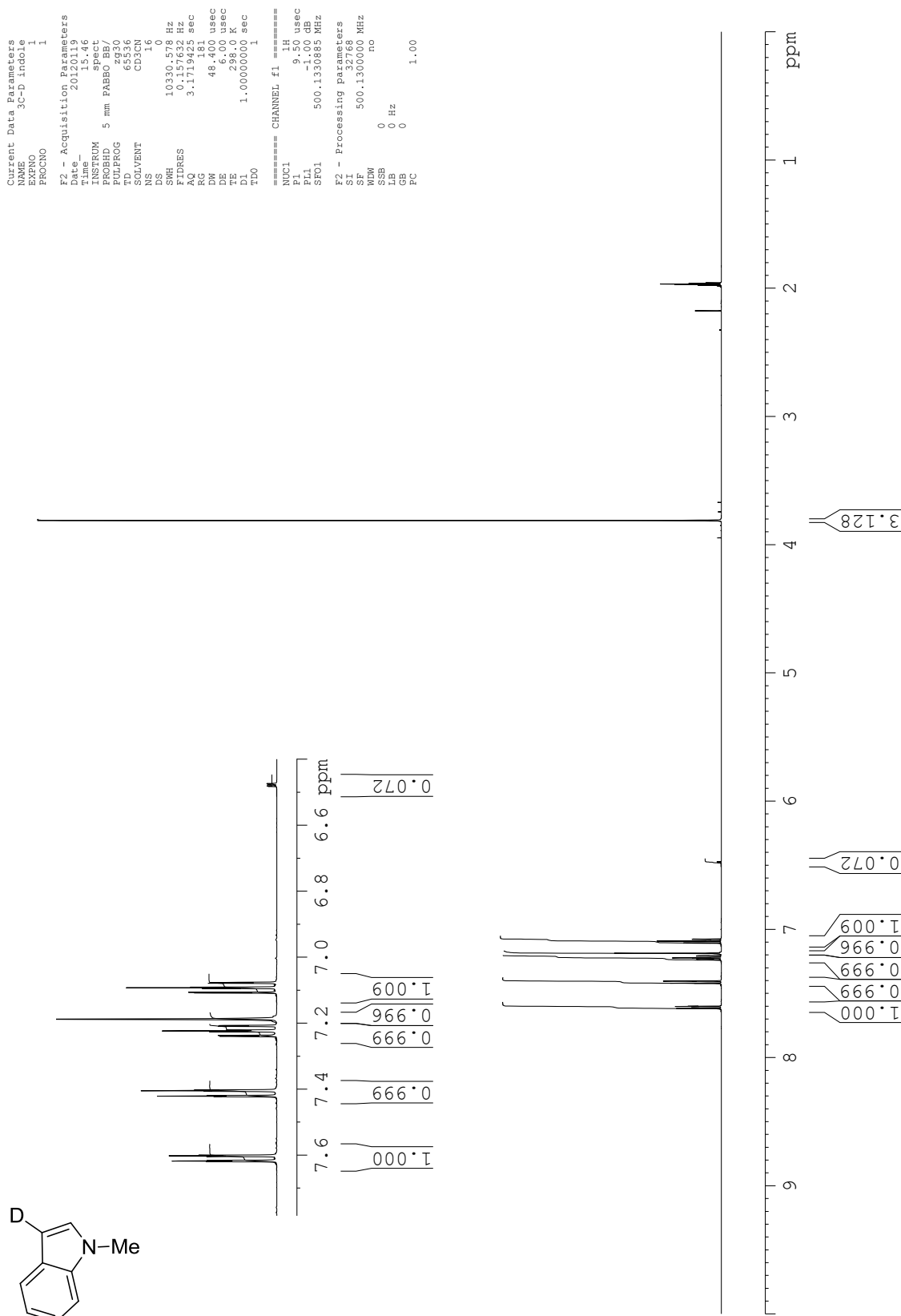
Atom	x	y	z	U(equiv.)
H(1)	1983	524	2027	108
H(2)	-1245	1752	854	111
H(3)	-465	948	1473	113
H(6)	2478	2676	997	69
H(8)	4361	908	2182	92
H(9)	5036	2372	1325	71
H(10A)	7171	2130	1785	143
H(10B)	6523	1485	1530	143
H(10C)	6411	1639	2220	143
H(11)	4745	2518	2583	64
H(14A)	5138	3647	405	116
H(14B)	4412	4268	673	116
H(16)	6893	3841	-293	98
H(17)	8535	4499	-737	122
H(18)	8982	5493	-353	119
H(19)	7937	5804	506	151
H(20)	6375	5125	984	151
H(22A)	6080	3473	3100	95
H(22B)	4488	3323	3314	95
H(23A)	4391	4285	3727	103
H(23B)	5942	4449	3481	103

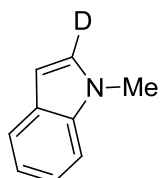
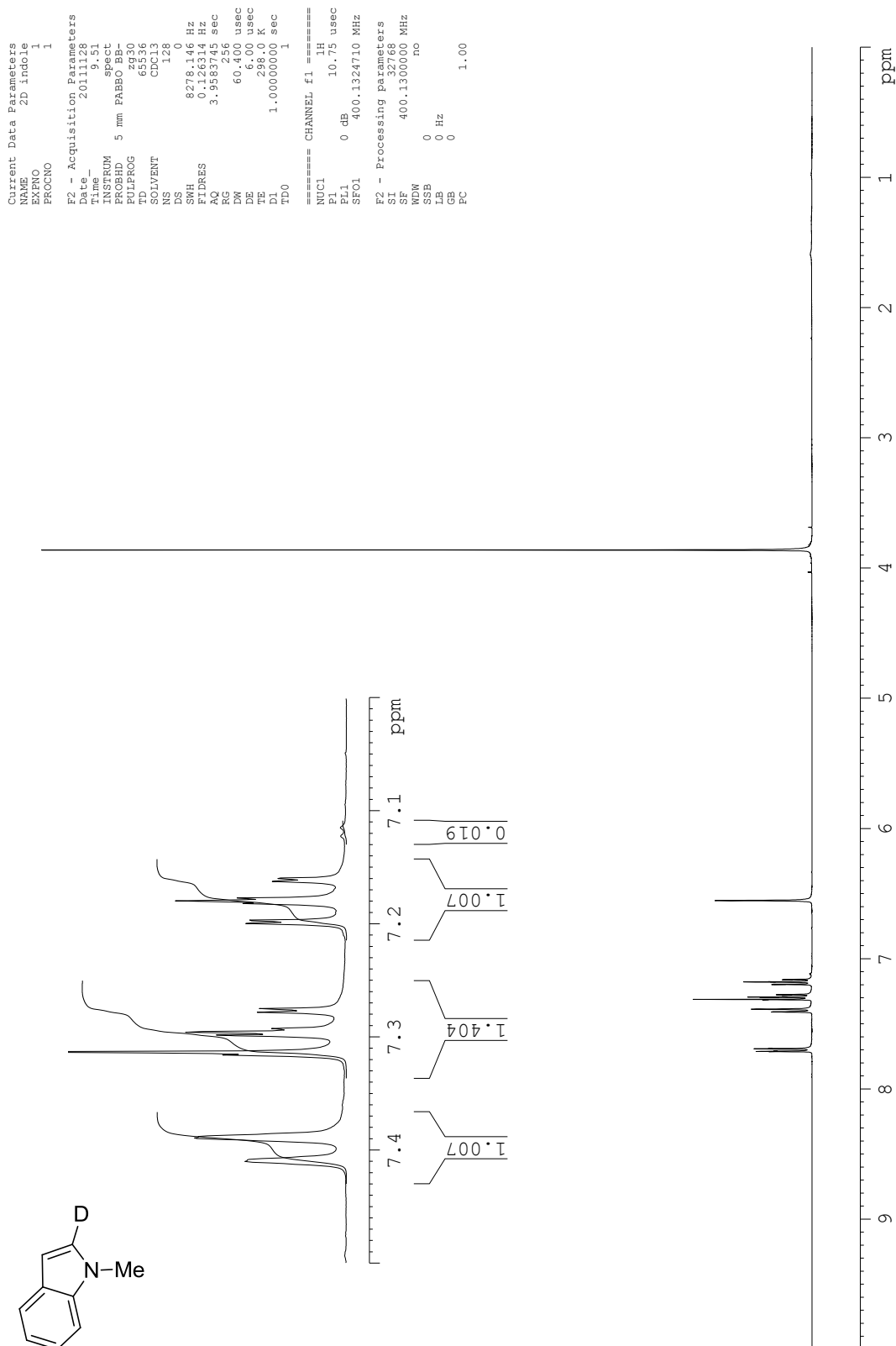
Table 6. Dihedral angles [$^{\circ}$] for **282**.

Atom1 - Atom2 - Atom3 - Atom4	Dihedral
C(6) - C(1) - C(2) - C(3)	-2.2(11)
I(1) - C(1) - C(2) - C(3)	178.2(6)
C(1) - C(2) - C(3) - C(4)	-1.7(12)
C(8) - N(1) - C(4) - C(3)	179.2(7)
C(8) - N(1) - C(4) - C(5)	-0.2(7)
C(2) - C(3) - C(4) - N(1)	-175.0(7)
C(2) - C(3) - C(4) - C(5)	4.3(11)
N(1) - C(4) - C(5) - C(6)	176.4(5)
C(3) - C(4) - C(5) - C(6)	-3.1(9)
N(1) - C(4) - C(5) - C(7)	-0.8(6)
C(3) - C(4) - C(5) - C(7)	179.8(6)
C(2) - C(1) - C(6) - C(5)	3.4(9)
I(1) - C(1) - C(6) - C(5)	-177.0(4)
C(4) - C(5) - C(6) - C(1)	-0.8(8)
C(7) - C(5) - C(6) - C(1)	175.5(6)
C(6) - C(5) - C(7) - C(8)	-175.1(6)
C(4) - C(5) - C(7) - C(8)	1.5(6)
C(6) - C(5) - C(7) - C(9)	6.5(9)
C(4) - C(5) - C(7) - C(9)	-176.9(5)
C(4) - N(1) - C(8) - C(7)	1.2(7)
C(5) - C(7) - C(8) - N(1)	-1.6(7)
C(9) - C(7) - C(8) - N(1)	176.6(6)
C(8) - C(7) - C(9) - C(11)	-98.2(7)
C(5) - C(7) - C(9) - C(11)	79.7(7)
C(8) - C(7) - C(9) - C(10)	24.1(9)
C(5) - C(7) - C(9) - C(10)	-158.0(6)
C(7) - C(9) - C(11) - C(12)	-116.2(6)
C(10) - C(9) - C(11) - C(12)	119.4(7)
C(9) - C(11) - C(12) - N(2)	-172.7(5)
C(9) - C(11) - C(12) - O(1)	7.7(8)
C(21) - N(2) - C(12) - C(11)	-165.2(6)
C(22) - N(2) - C(12) - C(11)	18.1(9)
C(21) - N(2) - C(12) - O(1)	14.5(8)
C(22) - N(2) - C(12) - O(1)	-162.2(5)
C(13) - O(1) - C(12) - C(11)	-107.4(6)
C(13) - O(1) - C(12) - N(2)	73.0(6)
C(12) - O(1) - C(13) - O(2)	3.2(10)
C(12) - O(1) - C(13) - C(14)	-177.6(6)
O(2) - C(13) - C(14) - C(15)	-6.5(13)
O(1) - C(13) - C(14) - C(15)	174.4(7)
C(13) - C(14) - C(15) - C(16)	118.1(8)
C(13) - C(14) - C(15) - C(20)	-63.0(11)
C(20) - C(15) - C(16) - C(17)	-2.4(12)
C(14) - C(15) - C(16) - C(17)	176.5(8)
C(15) - C(16) - C(17) - C(18)	-1.0(13)
C(16) - C(17) - C(18) - C(19)	2.8(15)

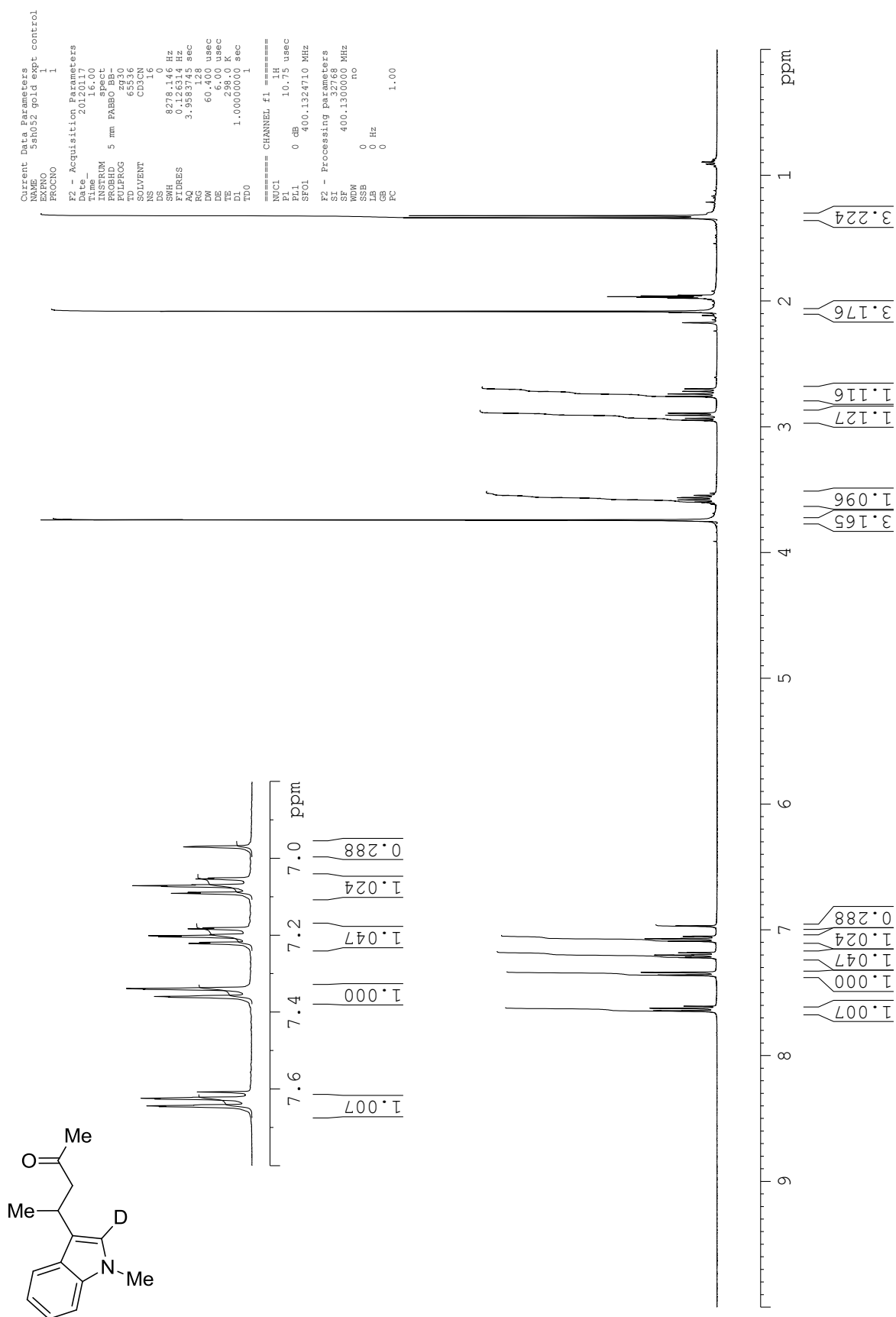
C(17) - C(18) - C(19) - C(20)	-1.0(17)
C(16) - C(15) - C(20) - C(19)	4.2(15)
C(14) - C(15) - C(20) - C(19)	-174.7(10)
C(18) - C(19) - C(20) - C(15)	-2.6(18)
C(23) - O(3) - C(21) - O(4)	179.6(8)
C(23) - O(3) - C(21) - N(2)	-0.8(9)
C(12) - N(2) - C(21) - O(4)	5.7(13)
C(22) - N(2) - C(21) - O(4)	-177.4(9)
C(12) - N(2) - C(21) - O(3)	-173.9(5)
C(22) - N(2) - C(21) - O(3)	3.1(9)
C(21) - N(2) - C(22) - C(23)	-3.8(8)
C(12) - N(2) - C(22) - C(23)	173.4(5)
C(21) - O(3) - C(23) - C(22)	-1.6(9)
N(2) - C(22) - C(23) - O(3)	3.1(8)

Symmetry transformations used to generate equivalent atoms:

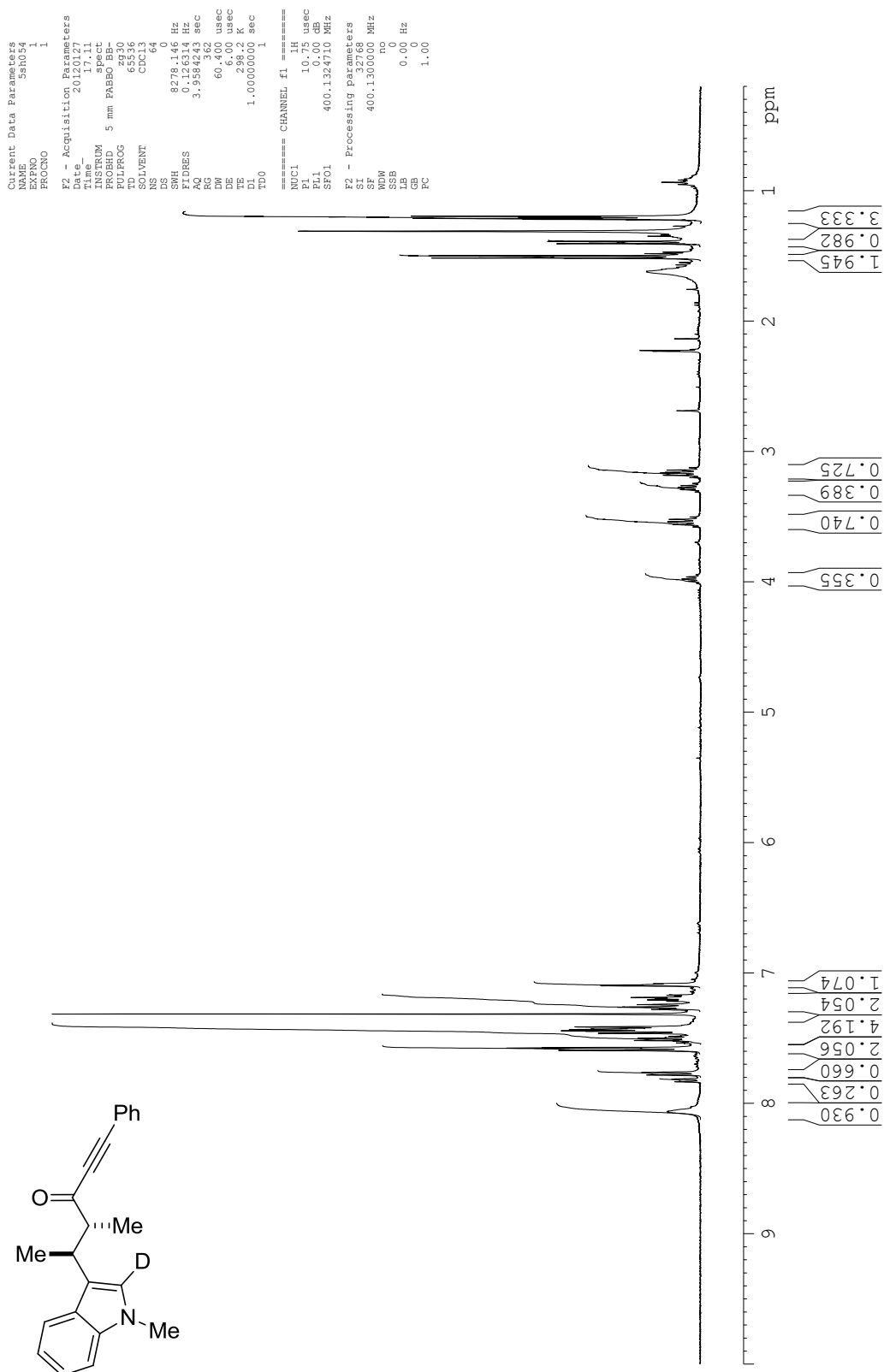
6.3 ^1H NMR6.3.1 C-3- ^2H -168

6.3.2 C-2-²H-168

6.3.3 222



6.3.4 218



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